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Vol. IV JANUARY, 1919 No. 4

The Journal of Laboratory and Clinical Medicine

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The Journal of Laboratory and Clinical Medicine

VOL. IV. ST. LOUIS, JANUARY, 1919 NO. 4

ORIGINAL ARTICLES

WAR DEAFNESS AND ITS PREVENTION—REPORT OF THE LABYRINTHS OF THE ANIMALS USED IN TESTING OF PREVENTIVE MEASURES.* (MIDDLE EARS PREVIOUSLY REPORTED)†

BY STACY R. GUILD, ANN ARBOR, MICH.

METHODS

A FULL description of the procedure by which each animal was handled at the time of exposure to the detonations was given in the report of the middle ear conditions; reference may be made to it for that part of the technic. In that report the protective measures tested were also listed and described. As stated there the animals were killed about 48 hours after exposure to the detonations. The treatment of the tissues at the time of killing the animals was directed primarily to the securing of the best possible cochlear fixation. The method used was the one with which I had had the best results in a series of experiments on cochlear histologic technic, conducted as a preliminary to objective work on the physiology of hearing which the war has postponed indefinitely, but which I hope at some future time to carry out. The fixation fluid used was Zenker-formol in the proportions suggested by Maximow (1909), as a modification of Helly's fluid, for other work. A stock solution is made in the following proportions:

Mercuric bichloride,	50 gm.
Potassium dichromate,	25 gm.
Sodium sulphate,	10 gm.
Distilled water,	1000 c.c.

*Submitted to the National Research Council.

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†Three previous reports have been made; the first was published in this JOURNAL, September, 1917; the second, January, 1918; and the third, March, 1918. The second report is the one containing the account of the middle ears the labyrinths of which are here reported.

This was filtered carefully to exclude any particles which might block small vessels. Just before using there was added to this stock solution 10 per cent by volume of 10 per cent formalin; the glacial acetic acid of the regular Zenker's fluid was not added. Both solutions were kept in an oven at 39° C. until the time of mixing for use. The fixative was injected through the vascular system, following a thorough washing out with a 0.75 per cent solution of sodium chloride, also kept at 39° C. until placed in the flask for injection. This preliminary washing out is essential for the securing of good penetration of the fixative.

The routine procedure was to place the animal under chloroform anesthesia; then to open the thorax and pericardial sac and insert the cannula of the injecting apparatus in the systemic aorta through the wall of the left ventricle, the ligature being placed by passing the thread through the transverse sinus of the pericardium, thus including the pulmonary aorta. This can be done very rapidly after a few trials and I was able regularly to have the saline solution running soon enough to avoid any clotting of blood in the cochlear vessels. The vessels to the caudal half of the body were routinely clamped off by a hemostat placed so as to include both aorta and inferior vena cava just above the diaphragm. This reduced the amount of fluid necessary for satisfactory injection of the cochlear region. The injection was made with air pressure averaging 145 mm. of mercury. About 150 c.c. of warm saline solution were used in washing out the blood and this was followed immediately by 200 c.c. of the warm fixative described above. Only a small portion of this reaches the cochleae, of course, since all the blood vessels of the upper half of the body are injected. The cochleae and some of the surrounding bone, including most of the vestibular parts, were then removed and the two pieces placed in 50 c.c. of warm fixing fluid and left at room temperature. These remained in the fixing fluid from a week to ten days, the fluid being changed two or three times, because a precipitate forms slowly after mixing the formalin with the Zenker stock solution. They were then washed for 24 hours in running tap water and placed in 10 per cent alcohol; and were transferred from this to 80 per cent alcohol by 10 per cent changes at 24 hour intervals. They were then placed in 80 per cent alcohol to which had been added a sufficient amount of a saturated solution of iodine in absolute alcohol to make the mixture a cherry red color. In this they remained until they ceased to decolorize the solution, more iodine being added as needed. This time averaged about ten days. They were then passed at 24 hour intervals through 90 per cent and 95 per cent alcohol into absolute alcohol which was changed three times. Instead of passing them directly into the mixture of equal parts of absolute alcohol and ether, they were passed through four intermediate mixtures, each increasing the ether ratio 10 per cent until the 50 per cent was reached. This was an extra precaution to avoid as far as possible shrinkages due to a more sudden change. Ordinary celloidin embedding followed, slow evaporation being used, taking a month or more to reach a firm consistency. The blocks were then hardened in 80 per cent alcohol and transferred through 50 per cent and 30 per cent alcohols into 4 per cent nitric acid for decalcification. They remained in this 12 days, except two

groups, one of which remained 6 days and the other 9 days. The fluid was changed daily. They were then transferred to a 5 per cent solution of sodium sulphate, remaining in this 48 hours with one change of fluid; and were then washed in running tap water for 24 hours. The blocks were then "double embedded" in paraffin. They were passed from the tap water through 30, 50, 80, and 95 per cent alcohols, and the dehydration completed with carbol-xylol (crystal carbolic acid one part, xylol three parts). Absolute alcohol can not be used because of the celloidin present. An intermediate step of equal parts of 95 per cent alcohol and carbol-xylol was used to make the change more gradual. After dehydration with carbol-xylol they were changed to xylol and while thus cleared the blocks were trimmed in such a way that the position of the modiolar axis could be determined later for orientation of the sectioning. They were infiltrated and embedded in 52° C. paraffin in the usual way, the celloidin block containing the cochlea being handled as a piece of tissue.

This method gave in most cases a very fair preservation of the delicate epithelial structures in the cochlea; in a few instances it has failed, these are probably cases where the vascular injection did not penetrate well. The preservation of the tectorial membrane is poor by this method, it is usually found curled back in part of the turns, and it is not so thick as some methods show it to be.

From blocks prepared by this method it is possible to cut thinner serial sections than have usually been employed in studies on the cochlea. From such a block I have an unbroken series of 5 micra sections of a whole guinea pig cochlea, and I have cut some at 3 micra, but not a series. The material used in this study is cut in 7 micra sections; because of the shortage of glassware, especially of large cover-glasses, only every fifth section was saved. It would have been impossible to mount all the series otherwise. From the wide extent of the injured areas reported in the experiments of Wittmaack, Yoshii, and others, it was thought that every fifth section would be sufficient to fully indicate the extent of the injuries. For an exact study of the distribution of injury that I have found unbroken series are needed; every fifth section gives the general distribution of injured areas, but the study of unbroken series might yield additional facts of interest. The sectioning was done with a sliding microtome, using the "water-on-the-knife" method. The blocks were oriented so as to parallel the modiolus as nearly as possible in sectioning; in most cases this was closely approximated, in a few there was some deviation. In most blocks the sectioning was continued until the stapes was reached; in some it was forced to stop sooner either because of imperfect decalcification of the block or because of hard particles in the niche of the round window or elsewhere in this region; these particles are probably grains of sand from the tap water, which was unusually laden with dirt at the time part of the washing was done. The sections were fixed to slides by the usual water-albumen paraffin section method, and were stained with Heidenhain's iron lac hematoxylin; counterstained with benzopurpurin, and mounted in damar. The technic differed from the usual treatment of paraffin sections on slides only in the use of carbol-xylol, instead of absolute alcohol, in passing from xylol to 95 per cent alcohol and back again.

This was necessary because of the celloidin present. To completely remove mercuric crystals the sections were passed through an iodine solution in 80 per cent alcohol before the transference to iron alum. The benzopurpurin was used in solution in 95 per cent alcohol; the sections permitted to overstain, and the excess stain removed by fresh 95 per cent alcohol; the slides being transferred to carbol-xylol to stop the decolorization at the desired stage.

RESULTS

The condition of the labyrinthine parts, here reported, should be compared with the middle ear conditions, previously reported; this can readily be done for the individual ears, as the animal designation has been made in all tabulations.

The injuries to the inner ear have been, for the most part at least, limited to the cochlea. In no case were all of the special sensory areas in the vestibular part of the labyrinth sectioned, owing to the close trimming of the blocks necessary to save glassware. Of those sectioned, many of the maculæ acusticæ and some of the cristæ acusticæ have some shrunken hair cells, but I have no reason to believe that these are more than artefacts. The stapes was reached in the sectioning in 76 of the 92 cochleæ cut; of the 76, all but 10 are in the normal position. In each of these ten cases the annular ligament is broken and the base plate of the stapes tilted more or less into the vestibule. While this condition may be due to the detonations, I am inclined to believe that it was caused by accidents in handling at some time before the celloidin embedding, most probably during the removal from the animal. Therefore these displacements will not be considered further. In both ears of one animal no joint cavity is present about the base plate of the stapes, but this is not a condition which can be attributed to the detonation. The position of the membrana tympani secundaria, closing the fenestra rotunda, is normal, or nearly so, in all cases; it is slightly wavy in some, but no more so than the changing fluids might account for. In part of the membranes there is some edema evident, especially of the middle ear surface. Free blood cells and clots are present on the middle ear surface, but these are the result of the damage to the middle ear parts, already considered. None of the labyrinths have what may be called "gross" lesions, such as the rupture of the walls of the ductus cochlearis or the scala vestibuli or the scala tympani. The occasional bending of parts of the basilar membrane occurs as often in controls as in exposed animals, and is probably due to the embedding. Definite lesions of the organ of Corti and of the spiral ganglion are present in many of the cochleæ. No evidence of extensive internal hemorrhage was found in any of the labyrinths; in some a few isolated blood cells were observed adhering to the scala tympani surface of the basilar membrane. (See Figs. 10 and 13.)

To present the appearance of the lesions observed drawings will be used; they are selected to show the more usual types of injuries.

In speaking of the turns of the cochlea the method of designating by half-turns, beginning at the basal end, has been selected as best adapted to the purposes of this report. Fig. 1 shows in outline a modiolar section with the turns numbered according to the method used. The part in the midmodiolar section

is considered as the middle of each half-turn; the junctions of the half-turns have the organ of Corti cut tangentially. Such junctions may be seen in Fig. 2. In speaking of sections of the organ of Corti the term "radial" refers to those in the region of the modiolar sections; the term "tangential" refers to sections in the region of the junction of two half-turns; the term "oblique" refers to sections in the intermediate region. Fig. 3 is of a normal organ of Corti in radial section, Fig. 4 is of a normal organ in oblique section, and Fig. 12 is of a normal organ in tangential section. The oblique and tangential sections are favorable for the observing of certain of the lesions because several of each element of the organ of Corti are included in each section. The first part of the first half-turn which deviates from the axis of the cochlear spiral and is almost parallel to the modiolus for a distance in the vestibule, has been listed separately in the records made; it is termed the "vestibular part"; Fig. 2 shows the relation of this part of the ductus cochlearis to the rest of the labyrinth. The fenestra rotunda is "beneath" the last portion of the vestibular part.

Figs. 3 to 14, inclusive, are at the same magnification—295 diameters; they are therefore directly comparable, and are at a magnification sufficient to permit ready recognition of parts. The normal sections are inserted for comparison with the injured ones.

The loss of single or of a few adjacent outer hair cells is the definite injury of most frequent occurrence and is evidently the least severe of the definite lesions. Figs. 6, 7, 8, and 13 show sections having such lesions in radial, oblique, and tangential sections. Special features in the various sections are mentioned in the legends (q.v.). Such loss of hair cells is usually associated with a displacement of the corresponding Deiters' cells, frequently showing as a nuclear displacement, as in Fig. 7. Derangements of Deiters' cells without loss of hair cells have not been called injuries in the records made for the reason that they may possibly be artefacts. For some time I was not certain that the absence of isolated hair cells indicated an injury, but after finding such gaps in many of the best preserved cochleæ I have arrived at the conclusion that these are not artefacts. This belief is further strengthened by the increasing frequency of such absences as an area of more severe injury is approached in following the organ of Corti in serial sections. As may be seen in the illustrations given it is possible to have several degrees of severity of such injuries, depending on the proportion of outer hair cells which are missing. It ranges from the loss of a single cell in one section with all the other sections of the region normal, up to the loss of the majority of the cells in all sections for a considerable distance. All these various lesions I have grouped under the term of first degree injury, which may be defined as the loss of part of the outer hair cells with or without derangement of the Deiters' cells.

The absence of all the outer hair cells is the condition found next in order of frequency to the preceding. Fig. 8 illustrates this lesion. This condition may be present in all the sections of a half-turn or more; it ranges from this large extent to a single section. Since only every fifth section has been saved, the presence of this condition in a single section of a series means that it may have

extended over any or all of the four sections to either side which were not saved. It will be noted in the illustration that the organ of Corti retains its general outline; this is one of the differentiating points between this injury and the more severe types. This condition, absence of all outer hair cells with retention of the general shape of the organ of Corti, has been termed second degree injury, for purposes of reference.

Of less frequent occurrence than the preceding condition is that illustrated in Fig. 9. Not only are the outer hair cells missing but also the organ of Corti is crushed out of shape; the illustration shows the usual condition of the filling of the tunnnel, Nuel's space, and the outer tunnel space with cellular debris. In some cases there is more or less vacuolization of the mass. It will be observed that the inner hair cell is present, as it is in the other lesions so far described. This condition does not, in my material, occur in isolated sections, but areas so injured are always adjacent at one end, and usually at both, to areas of lesser or of greater injury. This condition, absence of outer hair cells associated with a general crushing of the organ of Corti with massed or vacuolized debris in the large spaces of the organ, has been termed third degree injury.

A more severe lesion of the organ of Corti is that illustrated in Figs. 10 and 14. In this lesion the outer hair cells are all absent, the organ of Corti is badly broken up, the cellular debris is usually vacuolized but may be massed as in the typical third degree injury, and the inner hair cell is absent. The cells of the internal spiral sulcus are frequently vacuolized. This condition has been termed fourth degree injury, and is characterized by the severe disintegration of the organ of Corti with absence of the inner hair cell, which is, of the special sensory epithelial cells, the least often missing. In only one instance was the inner hair cell observed in an abnormal condition when the rest of the organ of Corti in that section was normal. Two adjacent sections of a series (every fifth section saved) show a chromatolysis of the inner hair cell. In one of these two sections there is no other injury evident; the other section has part of the outer hair cells missing. Elsewhere definite lesions of the inner hair cells have been observed only in association with severe injuries to the rest of the organ of Corti. This fourth degree injury, like the third degree, is not found in isolated sections in otherwise normal areas, but areas of it are bounded by areas of lesser degree of injury.

Fig. 11 shows the most complete destruction of the organ of Corti which is present in my material; it occurred in a zone of fourth degree injury, and since it occurred but once I have not given it a special designation of degree.

The distribution of the lesions of the organ of Corti in the various cochleæ studied is shown in the charts of Plate IV. In making these charts the relative lengths of the various half-turns have been approximated, instead of showing each half-turn as of the same value. To indicate the various degrees of injury three shades of grey, parallel lines, and dots have been used. The darkest shade of grey represents the condition that has been termed fourth degree injury; the intermediate grey, third degree injury; and the light grey, second degree injury. The narrowest of these light grey zones represent single sections, though they are proportionately too wide for the actual ratio which

a single section should cover in the chart. The parallel lines indicate areas where all sections are in the condition termed first degree injury; and the dots indicate first degree injury in isolated sections. Where two or three adjacent sections are in this condition it has been shown by drawing a line underneath the dots, unless it is between zones of more severe injury, in which case parallel lines have been used. The number of dots is not, in most cases, the exact number of sections with lesions but the number of dots indicates the relative frequency of sections showing injury to the organ of Corti. Since only every fifth section has been saved, the absolute distribution can not be determined from these series. The position of the ends of the injured areas can be determined only by means of graphic reconstruction which allows for the difference in length of the part of the organ of Corti contained in radial, oblique, and tangential sections. I have devised a suitable method for making such graphic reconstructions, but have not used it here since most of its value over the method of approximation would be lost due to having only every fifth section. In studying the cochleæ the organ of Corti and other structures were followed section by section from the vestibular end of the cochlear duct to the apical end, being traced back and forth through each series for the different turns. The notes, from which the charts presented were made, were jotted down at the time of observing injured areas during these examinations of series.

For convenience of reference, the conditions recorded have been grouped in four charts.

In Chart I are placed all cases where the outer ear was entirely open and the detonation used was one shot from a 45 caliber Colt automatic pistol with the muzzle at 15 cm. from the ear. Most of these are the open ears of animals in which the other ear was "protected;" in all cases the 15 cm. was measured from the opposite ear, and the barrel pointed downwards about 20 degrees along the left side from above and in front.

In Chart II are presented the controls with the open rubber ear and glass tubes of various sizes. From a study of the great variations in individual cases in the cochleæ recorded in Chart I, where all were exposed to as similar traumatic conditions as possible, it is evident that the number of controls with each tube is too small, there being only one with each, except with the 2 mm. tube, and in this case the extra two animals were used because wax entered the end of the tube during the experiment (cf. middle ear observations).

In Chart III are presented the conditions of the cochleæ of the "protected" ears. To facilitate comparison, these have been arranged in the same order as the middle ear observations on the protected ears (q.v.).

In Chart IV are presented the conditions of the cochleæ of animals submitted to detonations other than the usual one shot at 15 cm.

Besides these, two animals were taken as controls of the possible injury to the ears while in the basket during the experiment with others. One of these, animal 62, was also placed in the holding apparatus as a control of possible injuries by this procedure. The other, animal 63, simply remained in

the basket during six experiments, being exposed thus to the sound of six shots from the pistol at a distance of about 25 feet, the gun pointing away from the basket. Both cochleæ of animal 62 are entirely normal. The left cochlea of animal 63 has a few sections with missing or distorted outer hair cells in the sixth half-turn; the right cochlea has about 30 isolated sections with some outer hair cells missing, scattered throughout its length except in the vestibular part and the eighth half-turn; the injured sections are most numerous in the third to the sixth half-turns.

Shrinkage and chromatolysis of part of the cells in parts of the spiral ganglion are present in many of the cochleæ; this condition is present most often in the vestibular part and first half-turn; less frequently it is present in the second, third and fourth half-turns, and occurs very seldom above this level. In general the distribution corresponds with the injuries to the organ of Corti, but there are many exceptions to this general arrangement. In the vestibular part and first half-turn shrunken ganglion cells are much more frequently present in the cochleæ of unprotected ears than the protected ones in which definite lesions of the organ of Corti occurred; and in these unprotected ears the number of shrunken ganglion cells frequently appears to be a much greater proportion of all the cells than the proportion of hair cells missing in the corresponding region. On the other hand, in many cases the ganglion cells show no injury in regions corresponding to parts of the organ of Corti that were severely injured. The possibility must always be kept in mind that these ganglion cell alterations may be artefacts; but after observing many cases where the occurrence of a zone of injury corresponds to a zone of ganglion cell shrinkage and protoplasmic change I am of the opinion that these indicate a true lesion. Animals allowed to live a longer period of time after being submitted to detonations are needed to definitely settle this point. In two cases all the ganglion cells were in bad condition, but in both of these the general fixation was so poor that the alteration is in all probability an artefact. In a few cases some of the nerve fibers leading from the ganglion to the organ of Corti are definitely degenerating; in most cases they appear nearly, if not entirely, normal. The fibers in the organ of Corti itself can not be seen in the sections of the more severe lesions.

A peculiar condition is present in the cochleæ of animal 44. The ductus cochlearis, sacculus, and utriculus are distended to an unusual size. Reissner's membrane is bulged into the scala vestibuli and is longer than normal. It is not thickened. The walls of the utriculus and sacculus are similarly distended. The distention is somewhat less in the right cochlea. The right cochlea of animal 37 has a similar, but much less distended, condition from the basal end to the fifth half-turn, and the second and third half-turns of animal 27 show it in slight degree. In the one with the greatest distention, the left cochlea of animal 44, the stria vascularis of most of the third half-turn and of part of the first half-turn has a peculiar enlargement of the blood vessels. The enlargement of the blood vessels of the stria vascularis and the distention of the endolymphatic channels of the left cochlea of animal 44 may

be associated as cause and effect but it seems doubtful in view of the facts that enlarged vessels are not present in the other cases of distention and that several cases of enlarged vessels, though of much less extent, are present in cochleæ where no distention has occurred. I wish to specifically state that I am undecided whether either the enlargement of the vessels of the stria vascularis or the distention of the endolymphatic channels has been caused by the detonations.

DISCUSSION OF RESULTS

In discussing the above observations upon the labyrinths their bearing upon the relative efficiency of the various protective measures will be considered first and the evidence from the three sets of observations which I have made correlated. Then a comparison will be made of the lesions in my material with those recorded by other observers upon detonation injuries of the labyrinth, and the bearing of the results upon the general problem of the physiology of hearing indicated.

I. *Relative Efficiency of Protective Measures.*—The condition of the middle ear parts and the tambour results, reported previously, both indicated a division of the protective measures into two distinct groups on the basis of their relative efficiency in preventing the passage of the force of the detonation waves used; these two sets of results agree in the devices which would be placed in each group. Dry cotton, the Elliott protector, and the Wilson-Michelson instruments are in the less efficient group. Examination of Chart III shows that the division into groups on the basis of the cochlear results is not so well marked; each of the protective measures failed to prevent definite cochlear lesions in one or more of the ears with which it was used. Even here, however, a ranking of the devices is evident; and two of the three protective measures which are in the less efficient group on the basis of the other tests again rank lowest.

It may be that one of the groups of observations is of more value than the others; if so, this should receive the most consideration in drawing conclusions. I would call attention to the fact that the animal experiments are the ones which indicate the devices that permit an injurious amount of detonation waves to pass; the physical experiments are of value in helping to place the preventives in their relative order of efficiency. The tambour method, on the other hand, has the advantage which all experiments in physics have over biologic work; *i. e.*, the materials used are not subject to the individual variations which the reactions of living organisms are. It is evident from the great variations in the cochlear injury in the cases where the ear was open and the conditions were as similar as possible that there is either a great individual difference in guinea pigs in the degree of susceptibility to injury of this type or an entirely unrecognized factor acting to modify the detonations (see Chart I). In the conduction of the animal experiments with protective measures there are opportunities for errors in technic; they were recognized and guarded against, but the possibility must be kept in mind that in some cases the wax packing used may not have completely prevented the entry of injurious force through the

crevices around the tube which it was supposed to close, or that the device may not have been properly placed in the rubber ear. The former error is the more probable; the latter is one that is more likely to occur in the use of devices by troops than under laboratory conditions. If it were not for the great individual differences in the long series of controls (Chart 1), I would be inclined to think that the possible errors mentioned above had occurred often, and that therefore the cochlear results were almost worthless as a basis for comparison of the relative efficiency of the devices. But, if such were the case, the question immediately arises as to why the middle ears were not also damaged in a like ratio. As a possible explanation of the discrepancy here might be advanced the general belief for many years among otologists that in cases of air wave trauma of the ear the injury to the labyrinth is less when the tympanic membrane ruptures than when it remains intact; the explanation advanced is that the force is expended in rupturing the tympanic membrane. The statements are based upon clinical experience. Yoshii (1909) reported one animal which has a bearing upon the subject. In this case a guinea pig was exposed to the detonation from the firing of a revolver at 20 cm. (size of gun and position with reference to the animal not given). At autopsy it was found that the right middle ear was badly damaged while the left middle ear was entirely normal. Study of the cochleæ showed the right one to be entirely normal, while the left one showed "very light degree alteration." From his description the alteration is less than anything I have called a definite lesion. This case agrees with the clinical view. In my material, animals 17 and 18 were the only ones in which, under similar conditions for the two ears, one tympanic membrane remained intact and the other ruptured. In animal 17 the cochlea of the side with the normal middle ear was severely injured, while the other cochlea was only slightly injured. In animal 18 difficulties in technic prevent any definite statement as to the cochleæ. Since the tympanic membrane was ruptured in all cases of open ears exposed to the usual detonation, no comparison is possible in this series. However, there are many cases here, and in the controls with the open rubber ear and glass tube, in which the cochlea was severely injured. Of the ears with which dry cotton, the Elliott protector, and the Wilson-Michelson instrument were used, all had damaged middle ear parts; one of each group of three had the tympanic membrane ruptured, though less severely than in most of the cases of open ears. With dry cotton, the cochlea of the ear with a radial slit in the tympanic membrane is definitely injured; the injury to this cochlea is greater than to one of the other two, and less than the injury to the third one. With the Elliott protector the cochlear injury is much less in the case with a ruptured tympanic membrane than in the two where it remained intact. With the Wilson-Michelson device the cochlear injury in the case of the ruptured tympanic membrane is about the same as in one of the other two and less than the injury in the third case. With the rest of my material such comparisons can not be properly made, because the force of the detonation waves reaching the ears varied greatly, due either to different protectors or to dif-

ferent distances used. While some of my cases are in accordance with the idea that rupturing of the tympanic tends to protect the labyrinth, it seems to me, on the whole, that the exceptions to the rule are too numerous to accept it as an explanation of the inconsistency between the middle ear and the cochlear conditions. In this my material agrees with the clinical experience of Meyer with troops submitted to modern battlefield conditions. It seems improbable that a true "bone conduction" can have played much, if any, part here, since the vibrations would have had to pass through a person's body to reach the ground on which the animal rested.

The condition of the cochleæ of animal 63, used as a control for possible injury while in the stock basket during the testing with other animals (see page 159), was a surprise to me, as I fully expected this control to be normal; animal 62 had both cochleæ entirely normal. There is a possibility that the lesions present, outer hair cells missing in isolated sections, are not due to detonations, in which case all the lesions of this nature would have to be ruled out of consideration. On the other hand, if they are due to the detonations of the pistol at the distance at which the basket was placed, (25 feet with the gun pointing in the opposite direction), all the cases of such "isolated section" lesions must be considered as possibly due to such an origin and their bearing on the protection afforded by devices thrown out. At the time of the experimentation I considered the distance sufficient to avoid any such complication; at present I must leave the question of interpretation open. Here, as in the other groups, variation has occurred; one animal normal and one injured (?).

As the most suitable way of determining the ranking given by the combined tests to the protective measures, the method of adding the rankings given by the different tests has been chosen. All three sets of observations are given the same value by this method. The devices tested only by the tambour method are omitted in this tabulation. To determine the order of efficiency as given by the tambour method the results with the three guns used are ranked. When two devices are tied for a place, the sum of this and the next lower ranking is halved and each of the devices given this number. (See Tables I and II.)

The ranking arrived at by this method is open to criticism, and is, at best, only an approximation. The division into two groups is very definite, however; and the other requirements for military use should be the deciding factor in choosing from the more efficient group, rather than the slight differences in the laboratory results with these protective measures. These other factors have already been considered in the previous reports and need not be taken up here. It suffices to state that the "Tommy" is the best of the mechanical devices from the standpoint of general military requirements for field use by troops, and since it has a slight advantage over the others in the laboratory tests it is the protective measure which seems to be indicated for a large field trial. On the other hand, the results of the laboratory tests seem to eliminate the need of field trials by troops of dry cotton, the Elliott protector, and the Wilson-Michelson device.

II. *Comparison with Previous Work on Detonation Injuries.*—The extent and distribution of the injuries to the organ of Corti in the animals I have used are quite different from those reported by Wittmaack, Yoshii, and Prenant and Castex, but are similar to some of Hoessli's and of Hoshino's cases. With the exception of some of Hoessli's experiments all the animals used by other workers have been exposed to detonations with the ears entirely open. Wittmaack's statements are very indefinite regarding his detonation cases; some animals were negative, and no statement is made of the extent of the injured area in the ones which were injured. The one figure which he presented of a detonation injury is from the next to the highest turn (fifth and sixth half-

TABLE I

RANKING OF THE DEVICES BY THE TAMBOUR METHOD

PROTECTIVE MEASURE	RANKING ACCORDING TO			SUM OF RANKINGS	RESULTING RANKING
	22 CALIBER	38 CALIBER	44 CALIBER		
Vaselined cotton	1½	1	2	4½	1
"Tommy"	3	2½	1	6½	2
Glycerined cotton	1½	4	3	8½	3
Mallock-Armstrong	4	2½	5	11½	4
Wax cone	5	5	4	14	5
Wilson-Michelson	8	6	6	20	6½
Elliott Protector	6	7	7	20	6½
Dry cotton	7	8	8	23	8

TABLE II

RANKING OF DEVICES BY THE AVERAGE OF THE THREE SETS OF RESULTS

PROTECTIVE MEASURE	RANKING ACCORDING TO			SUM OF RANKINGS	RESULTING RANKING
	TAMBOUR METHOD	MIDDLE EAR CONDITIONS	LABYRINTH CONDITIONS		
"Tommy"	2	1	4	7	1
Mallock-Armstrong	4	2	3	9	2½
Glycerined cotton	3	5	1	9	2½
Wax cone	5	3	2	10	4
Vaselined cotton	1	4	6	11	5
Elliott Protector	6½	7	7	20½	6½
Wilson-Michelson	6½	6	8	20½	6½
Dry cotton	8	8	5	21	8

turns of my terminology); it resembles somewhat the lesion I have termed third degree injury. A study of this and other figures given by Wittmaack leads me to agree with the group of workers in Siebenmann's laboratory at Basel; *i. e.*, there are many artefacts due to faulty histologic technic in the work of Wittmaack, so that even his indefinite statements must be discounted. As in all of his work on cochlear injury by sound waves Wittmaack considered the injury to the ganglion cells the primary lesion and the epithelial degeneration secondary. The lesions found by Yoshii in the middle ears were very similar to those of my unprotected animals. The two figures given by him of the organ of Corti after exposure to single detonations show a condition which agrees with that which I have termed fourth degree injury. (An ex-

tensive quotation from Yoshii's description of the lesions observed by him was given in the report on the literature, page 851 of the September, 1917, Journal of Laboratory and Clinical Medicine, to which the reader is referred.) He reported this severe lesion as present the whole length of the cochlea, which is a lesion more extensive than is present in any of the animals I have used. He also reported changes in the ganglion cells, and he, like the rest of the Siebenmann group of workers, considered these to be secondary degenerations and the epithelial primary. He also mentioned hemorrhage into the spaces of the labyrinth in some cases. The size of the gun used by Yoshii was not definitely stated; he merely said, "Diese Versuche wurden teils mit einer Kinderpistole und blossen Zündhütchen, teils mit Revolver und Patronen unmittelbar vor der Ohrmuschel und zwar jeweilen an beiden Ohren rasch nacheinander ausgeführt." He placed the muzzle of the gun much closer to the ear than I did, and in reality exposed each ear to two detonations; for my experiments show that both ears are damaged at much greater distances than that between the two ears of the guinea pig. This closer range may account for the more extensive injury his animals received. He used eight animals in this series; two were killed immediately, and one each after 2, 3, 8, 25, 45, and 60 days respectively. In view of my results it seems probable that more animals might have given him more variation. In any case, his statements as to some regeneration having occurred in the animals killed after the longer intervals certainly needs confirmation with a greater number of animals for each stage.

Hoessli, in his first series with detonations, was testing primarily air and bone conduction, to determine which transmits the injurious force. He used three guinea pigs with the incus removed on the left side of each, and two animals with moistened cotton in both ears. All were placed in a cage and a Swiss army revolver was fired five times at about 30 cm. above them. They were killed 24 hours later. Each animal was reported by a separate protocol. In none of the cases was there any damage to the middle ear parts, other than the operative injury in the animals with the incus removed. All three of the cochleæ in the cases with the incus removed were normal, as were also three of the four ears which had moistened cotton in the external meatus. In two of the three open ears with normal middle ear parts and one of the cotton protected ears the cochleæ had lesions in the organ of Corti in the lower half of the second turn (third half-turn of my terminology). The injury as described agrees with what I have termed third degree injury; Hoessli noted that the inner hair cells were present, and stated that there was no evidence of injury to the ganglion cells or nerve fibers, except the fibers in the organ of Corti itself. Except for this half-turn he reported the cochleæ normal. Of the third case of open ear with normal conducting apparatus, he said: "Die Scala cochleæ ist im ganzen normal und zeigt keine Veränderungen. Einzig an derjenigen Stelle, wo wir in Fall 22 die ausgedehnten Veränderung vorfinden, sehen wir hier einen teilweisen Mangel der äusseren Haarzellen bei sonst normalen Cort. Organ. Die übrigen Skalateile

sind ebenfalls normal." Apparently this was a slight injury; Hoessli was properly very cautious as to the interpretation of possible artefacts. In those of Hoessli's cases which are comparable to mine, cochlear injuries occurred in the same region where mine show the most frequent injury; *i. e.*, the third half-turn. The condition of the unprotected middle ear parts in his cases shows that he was working with a less powerful wave than I have used, for no injury to the middle ear parts occurred. Hoessli believed that the one case where the wet cotton failed to protect was due to the scratching loose of the cotton by the animal. He followed this series by one in which he used four cats, the left ears stopped with wet cotton, the right ears left open. To prevent scratching out of the cotton the animals were lightly narcotized and five shots were fired at 25 cm. above the four of them. As before, the animals were killed 24 hours later. The left ears in all cases were normal. In three of the four right ears there was an area in the upper part of the basal turn (upper part of second half-turn) extending through about 15 sections (thickness of sections not stated) where a slight variation from normal was found; the variation consisting of a depression of the organ of Corti in the region of the outer hair cells. The fourth case was entirely normal. In view of the variations in individual cases in the longer series I have used the two exceptions in Hoessli's short series are interesting.

While Hoessli was interested primarily in the question whether air or bone conduction transmits the injurious waves, he called attention to the bearing of the results with wet cotton to the protection of soldiers. All that he says of this phase of it is here quoted verbatim: "Hier denkt man unwillkürlich an die vielen Fälle von Schusstrauma bei Soldaten, welche Watte in den Ohren getragen haben sollen. Wir sehen eben hier, dass wenn der Wattepfropf nicht ganz fest sitzt, und am Ende gar nicht angefeuchtet ist, der Schutz des Ohres ganz illusorisch ist."

The region in which the majority of the lesions have occurred in my material is in general the same as was injured by the various guns used by Hoshino (1917).* He exposed guinea pigs to the detonations of a medium-sized revolver, a hunting gun, an army rifle, and a cannon. With the small arms blank cartridges were used and in most cases the shooting was directly toward the ear, at distances varying from "close up" to 100 cm.; two series were run with each gun, in the first group of series one shot was fired toward each ear of each animal, in the second group several shots each, the number varied from 5 to 350. The cannon was one used as a "time piece" and was loaded with only about four pounds of powder; the animals were placed two meters in front of the muzzle; they were blown as much as twenty meters by the explosion. Two animals were exposed to one shot each and two to five shots each. The animals of the various series were killed at intervals varying from "immediately" to fifty days after exposure. The greater number of animals were handled by an injection fixation, using Held's formal-bichromate-acetic

*It is to be regretted that the observations of this Japanese otologist are recorded in a language which renders them inaccessible to so many investigators. I desire to here express my thanks to Dr. I. Watanabe, an assistant in this laboratory, for reading this article to me.

mixture. The resulting injuries to the labyrinth were more severe and widespread in the cases where many shots were fired than in those "once exposed" (really twice since each ear was considered separately in counting the shots), but were in the same region of the cochlear canal for each gun, whether one or many detonations were used. Hoshino reported that the region of most severe injury varied for the different guns; it was lowest for the cannon and highest for the revolver. The regions for each were: (1) revolver, second turn and lower part of third; (2) cannon, upper part of basal and lower part of second turn; (3) army rifle, upper part of basal turn; and (4) hunting gun, lower part of second turn. One monkey was used, it was exposed to one detonation from the rifle held close to the ear. The injured area extended the whole length of the cochlea in this case, but Hoshino thought the wide extent possibly due to the short distance rather than to the different type of animal. The injuries to the organ of Corti varied from minor atrophic changes to complete destruction and replacement by a simple epithelium. Hoshino also broke the tympanic membranes of six animals and introduced staphylococci into the middle ears, waited until a suppurative otitis had developed, and then exposed them to detonations from the small arms. He found in general the same type and extent of injury due to detonation as in the animals with normal middle ears similarly treated. He added this suppurative otitis evidence in support of the view that impaired conducting apparatus does not protect the labyrinth from detonation injuries. Hoshino reported lesions involving the tectorial membrane, which was sometimes "frayed out" and sometimes almost entirely missing. While the technic used on my material is not favorable for the study of the tectorial membrane, because of the way it is shrunken and frequently turned up even in normal cases, I have observed no evidence that it has definite lesions due to detonations. While Hoshino stated that the area injured was more extensive with repeated detonations than with one, he did not mention variations in extent under identical conditions, such as my material shows. The small amount of powder used in the cannon and the fact that no shell was used would indicate that the intensity of the detonation was not so great as that of the majority of artillery pieces and exploding shells, but the placing of the animals in front of the muzzle where they were hurled twenty meters by the explosion simulated to a degree the conditions in the battle field where men are frequently hurled by the blast of an exploding shell and at the same time exposed to the intense sound. It is of interest to note that the lesions produced by Hoshino's cannon were of the same nature as those produced by the smaller detonations of both himself and others; this indicates that the study of lesions due to relatively small detonations are of value in interpreting the effects of more intense explosions.

Prenant and Castex (1916) placed animals in cages near large caliber guns at Fontainebleau. In no case was the tympanic membrane ruptured or the middle ear inflamed; ten guinea pigs and six rabbits were used. The preservation of the labyrinths was poor; they reported extensive cochlear lesions of the type to be expected from previous work in this line with smaller

guns. Since this is the only work in which animal cochleæ have been reported after exposure to detonations of such large guns as they used, it is very much to be regretted that the histologic technic used gave such poor results, for this makes them of very little value except for very indefinite comparisons and conclusions.

The report of J. S. and John Fraser (1917), made upon autopsy material from soldiers deafened by detonations, must be considered in the light of the histologic technic employed by them, which was such as to render the results very indefinite, as they realized. Hemorrhage into the labyrinth and about the entrance of the nerve roots in the fundus of the internal meatus were definite findings of interest. It is almost impossible in their material to differentiate the artefacts from the actual lesions in the organ of Corti and nervous tissues. Wilson reported recently (*Journal of the American Medical Association*, August 24, 1918) the condition of a temporal bone secured at autopsy six hours after the death of a soldier who had been deafened by a shell explosion. (Wilson said that two were reported in the Harvey lecture which he gave; but this is not yet available to me.) Formalin fixation was used. He, like Fraser, reported hemorrhage in the base of the internal auditory meatus. There was very evident damage to the cochlear parts; edema and small cell infiltration were mentioned as being present in the ganglion, stria vascularis, basilar membrane and organ of Corti. The epithelial cells and the ganglion cells were "indistinct," doubtless due in part, at least, to the time after death before placed in fixative and to the necessarily slow penetration of the fixative, even though the superior semicircular canal was opened.

The presence in my material, except in the most severe injuries, and also in Hoessli's detonation cases, of the inner hair cells is interesting in connection with Hoessli's observations on injury by the sound from organ pipes; he found the inner hair cells intact after the outer hair cells had disappeared and even sometimes when the supporting apparatus of the outer hair cells had broken down. These facts indicate either that the inner hair cells are more resistant to injurious sound waves, or that they do not receive as great intensity of the waves as do the outer hair cells. This is not taken into account in any of the theories of hearing. The statement of Shambaugh (1911) that the ciliæ of the outer hair cells are in constant contact with the tectorial membrane while those of the inner hair cells are free is suggestive in this connection.

None of the reports of previous experimental work involving detonation injury of the cochlea make any mention of separated zonal lesions, which are so plentiful in my material. (See, for example, "34 Rt." in Chart I.) It is evident that if the variations in sound waves are perceived by any type of peripheral analysis, the occurrence of definite zones of injury to the organ of Corti indicates that the parts injured were most active in converting the sound waves into nervous energy. In other words, if either the Helmholtz theory in its original form or in any of its modifications, or the Lehmann or the Ewald or the Köhler theory, or the theories involving the tectorial membrane as a differentiating mechanism, are correct, injured zones of the organ of Corti

are to be interpreted as being in the areas of resonance for the sound waves that caused the damage. If there is any definite pitch, or if there is a mixture of vibration frequencies in the sound waves produced by the firing of a 45 caliber pistol, it seems reasonable to suppose that it will not vary with different shots to the extent that would cause the difference in cochlear lesions observed under otherwise identical conditions; that is, open ears at the same distance and direction from the gun. No attempt has been made to obtain and analyze sound curves from the detonations used, so that no conclusions can be reached along this line.

A general view of Chart I, in which are presented the cochlear conditions in the open ears exposed to the firing of one shot at 15 cm. from the muzzle of a 45 caliber Colt automatic pistol, reveals that the average center of the injured areas, other than isolated sections of first degree injury, is in the third half-turn, except for the few cases with severe injury in the vestibular part and first half-turn. The making of the charts with the relative lengths of the half-turns indicated permits the ready recognition of the fact that the center of the total length of the cochlear duct of the guinea pig is also in the third half-turn. In Chart III, in which are presented the cochlear conditions in the "protected" ears, the average center of the injured areas is somewhat higher; and there is almost complete absence of injuries, even of the first degree in isolated sections, in the whole of the basal turn (vestibular part and first and second half-turns) of all the cochleæ, except those in the Elliott and Wilson-Michelson series.

These observations of separated zones of injury and the average grouping of the same are presented and attention called to them in the hope that they may prove of value at some time, in connection with other data, in solution of the problem of the physiology of hearing.

It is a pleasure to express here my appreciation of the valuable suggestions made by my chief, Dr. Huber, during the course of this work.

RESUMÉ OF ALL MY REPORTS UPON WAR DEAFNESS AND ITS PREVENTION

1. Laboratory methods for the testing of measures for the prevention of detonation injuries to the ear have been devised and such tests have been carried out upon various protective measures.

2. These tests indicate that the measures tested may be divided into two definite groups upon the basis of their efficiency in preventing the passage of the force of the detonation waves used; the variations within each group are less decisive. In the more efficient group are the Scientific Ear Drum Protector "Tommy," the Mallock-Armstrong Ear Defender, cotton soaked with glycerine, cotton soaked with vaseline, and the wax cone of the Italian navy type. In the less efficient group are dry cotton, the Elliott Perfect Ear Protector, and the Wilson-Michelson device.

3. The cochlear lesions produced by the detonations differ in extent and distribution from those hitherto reported; the injury areas are frequently separated by normal zones; these lesions are recorded in a graphic form which

makes them more available for reference than if the usual method of written protocols had been followed. The facts are presented without drawing theoretical conclusions as to their bearing on the physiology of hearing.

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Explanation of Figures

ABBREVIATIONS

a., Apical end of ductus cochlearis.
c.C., Cells of Claudius.
c.D.c., Cuticular processes of Deiters' cells (basal part).
c.H., Cells of Hensen.
c.i.s., Cells of internal spiral sulcus.
f.r., Membrana tympani secundaria closing the fenestra rotunda.
g.sp., Ganglion spirale.
i.h.c., Inner hair cells.
i.p., Inner pillars.
l.o., Lamina spiralis ossea.
l.sp., Spiral ligament.
m.b., Basilar membrane.
m.ret., Membrana reticularis.
m.v., Membrana vestibularis (of Reissner).
n., Nerve fibers in the spiral osseous lamina.
n.c. Cochlear nerve.
n.D.c., Nuclei of Deiters' cells.
n.o.p., Nuclei of the outer pillar cells.
N.s., Nuel's space.
o.h.c., Outer hair cells.
*o.h.c.*1, Outer hair cells of the first row.
o.h.c.2, Outer hair cells of the second row.
o.h.c.3, Outer hair cells of the third row.
o.p., Outer pillars.
o.t.s., Outer tunnel space.
ph.pr., Phalangeal processes of Deiters' cells.
sac., Sacculus.
s.t., Scala tympani.
s.v., Scala vestibuli.
t.f., Tunnel nerve fibers.
t.s., Tunnel space of the organ of Corti.
utr., Utriculus.
v.p., "Vestibular part" of the ductus cochlearis.
v.sp., Vas spirale.

Legends for Plate I

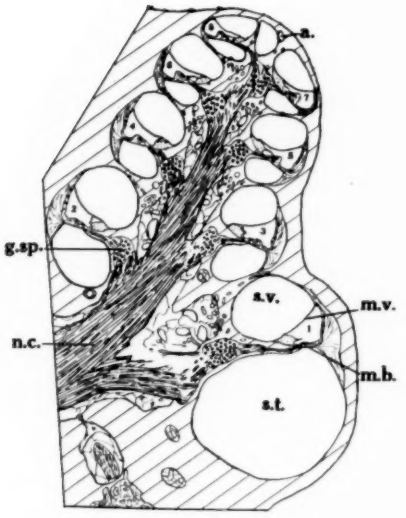
FIG. 1.—Outline drawing of a mid-modiolar section of a left cochlea of a guinea pig. Guinea pig 55, left cochlea, slide 1, row 4, section 1, 15×. The arabic numerals in the various sections of the ductus cochlearis indicate the designation of half-turns as used in this article. The part in the modiolar section is considered as the center of each half-turn; the junctions of the half-turns are in the sections which cut the curve of the organ of Corti tangentially.

FIG. 2.—Outline drawing of a section of a right cochlea of a guinea pig to one side of the modiolar axis, showing the position of what has been termed the "vestibular part" of the ductus cochlearis and the relations of parts in "oblique" and "tangential" sections. Arabic numerals as in Fig. 1. Guinea pig 21, right cochlea, slide 2, row 1, section 2, 15×.

FIGS. 3 to 14, inclusive, were drawn with the aid of a camera lucida at a magnification of 885 diameters, and have been reduced in reproduction to 295 diameters, one-third of the original size of the drawing. Being at the same magnification, comparison is facilitated. Figs. 3, 4, and 12 are drawings of sections of the organ of Corti in normal condition, and are presented for comparison with the ones having lesions. All the cochleæ were prepared by the same technic and the sections used for illustrations were selected to present the typical lesions observed. See the text matter for the technic and the terminology used in designating the lesions.

FIG. 3.—Drawing of a normal organ of Corti in radial section. Guinea pig 21, right cochlea, slide 1, row 4, section 8, second half-turn, 295×. As is well known, the shape of the organ of Corti varies in the different parts of the ductus cochlearis; allowance must be made for this in comparing this drawing with those of lesions in other parts of the cochlea.

FIG. 4.—Drawing of a normal organ of Corti in oblique section. Guinea pig 41, right cochlea, slide 1, row 5, section 2, second half-turn, 295×.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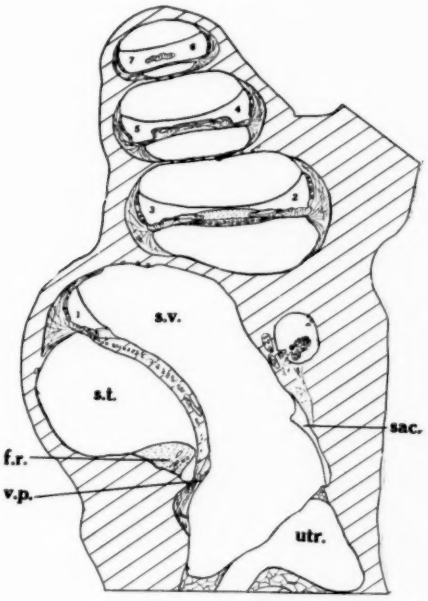
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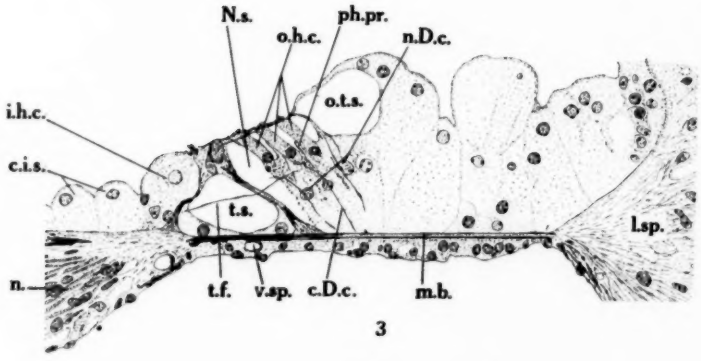
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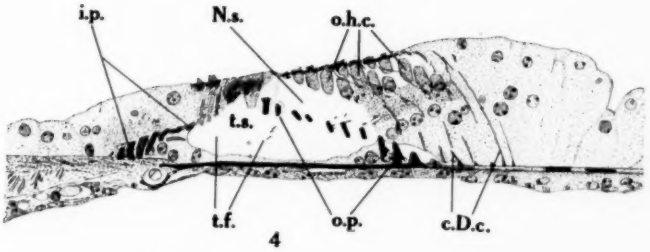
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Plate I.

Legends for Plate II

FIG. 5.—Organ of Corti, with first degree injury, radial section. Guinea pig 52, left cochlea, 1-4-7, third half-turn, 295×. The outer hair cells of the second and third rows are missing.

FIG. 6.—Organ of Corti, with first degree injury, radial section. Guinea pig 30, left cochlea, 1-6-2, first half-turn, 295×. The outer hair cell of the first row is absent, and the nucleus of the corresponding Deiters' cell is displaced downwards.

FIG. 7.—Organ of Corti, with first degree injury, oblique section. Guinea pig 47, right cochlea, 1-5-5, second half-turn, 295×. Compare with Fig. 4. Some of the cells of each row of outer hair cells are missing.

FIG. 8.—Organ of Corti, with second degree injury, radial section. Guinea pig 40, left cochlea, 1-3-2, fourth half-turn, 295×. All the outer hair cells are missing and the Deiters' cells are partially destroyed. Note that the general shape of the organ is retained; it is different from that of Fig. 3, but is the normal outline for this part of the cochlea.

FIG. 9.—Organ of Corti, with third degree injury, radial section. Guinea pig 29, left cochlea, 1-3-6, fourth half-turn, 295×. The shape of the organ is lost, being crushed; there is cellular debris in the spaces of the organ; the outer hair cells are missing; the reticular membrane in this case is broken and pieces of it are seen scattered through the mass.

FIG. 10.—Organ of Corti, with fourth degree injury, radial section. Guinea pig 28, left cochlea, 1-4-2, third half-turn, 295×. The severity of this type of lesion may be seen at a glance; all the essential parts of the organ of Corti have been destroyed. Adhering to the scala tympani surface of the basilar membrane may be seen two red blood cells and one leucocyte; this is one of the few cases where even this much hemorrhage was observed.

FIG. 11.—Drawing of a section in which the organ of Corti has been almost entirely replaced in 48 hours by a simple epithelium. Guinea pig 50, left cochlea, 1-4-9, third half-turn, 295×. This is the only instance in my material in which the destruction is so complete. I have not given it a designation of degree as was done with the types of lesions which occurred often.

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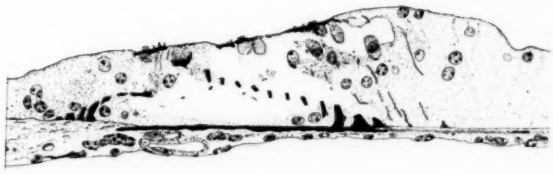

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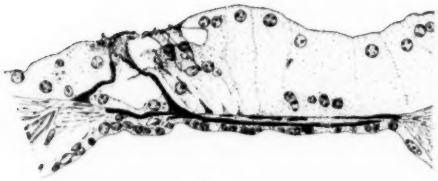

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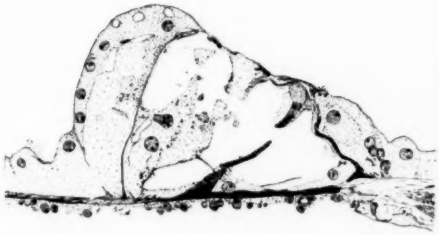

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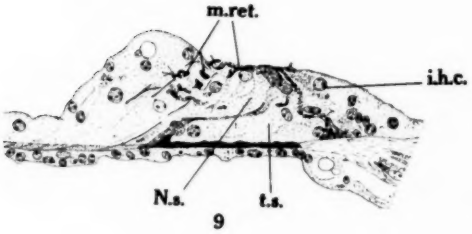

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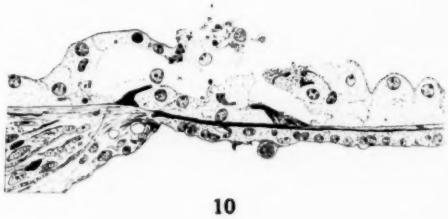
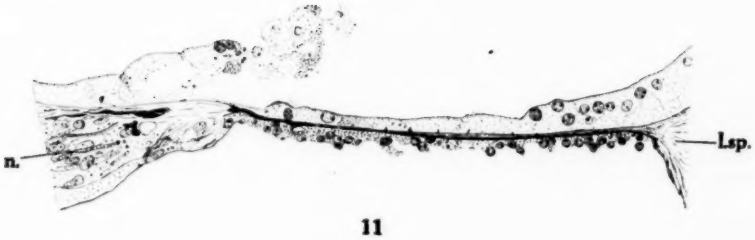


10



11

Plate II.

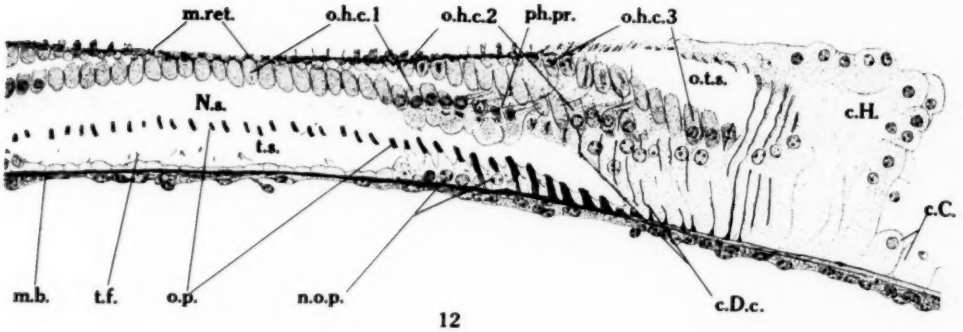
Legends for Plate III

FIGS. 12, 13, and 14 should be compared directly in order to interpret readily the lesions shown in 13 and 14. All three are drawings of sections which have been selected as being of corresponding parts of the various organs of Corti. The elements of the organ of Corti have been labelled in Fig. 12 only; reference should be made to it in studying Figs. 13 and 14. Oblique and tangential sections are favorable for observing lesions because of the number of each element present in a single section.

FIG. 12.—Normal organ of Corti in tangential section; the plane of section is parallel to the modiolar exis. Guinea pig 33, left cochlea, 1-5-6, junction of fourth and fifth half-turns, 295×.

FIG. 13.—Organ of Corti with first degree injury, tangential section. Guinea pig 27, left cochlea, 1-5-2, junction of fourth and fifth half-turns, 295×. When compared with Figs. 5 and 6, which are of radial sections of the organ of Corti, the nature of this lesion is better understood; a few or even single outer hair cells are missing in a place. Such lesions are not artefacts due to the dropping out of bits of the tissue during or after the sectioning, since the pieces are embedded in celloidin and there is no evidence of such vacancies in the celloidin, which is itself faintly stained and would therefore show gaps.

FIG. 14.—Organ of Corti, with fourth degree injury, tangential section. Guinea pig 28, left cochlea. 1-2-7, junction of third and fourth half-turns 295×. Compare with Fig. 10, which is of this type of lesion in radial section. Comparison with Fig. 12 emphasizes how much destruction has occurred.



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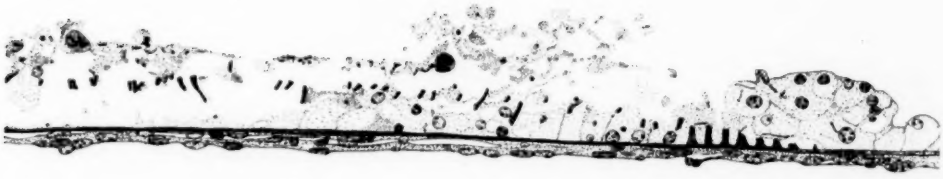
13



14

Plate III.

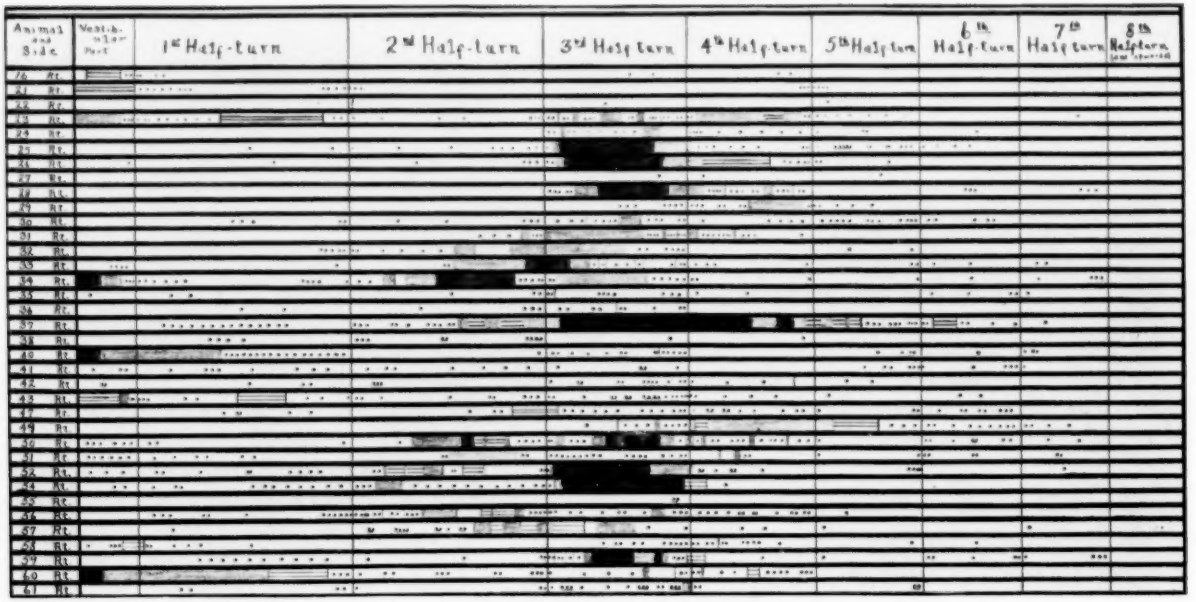


Chart I—Plate IV.

Chart II—Plate IV.

(For description of charts see page 180.)

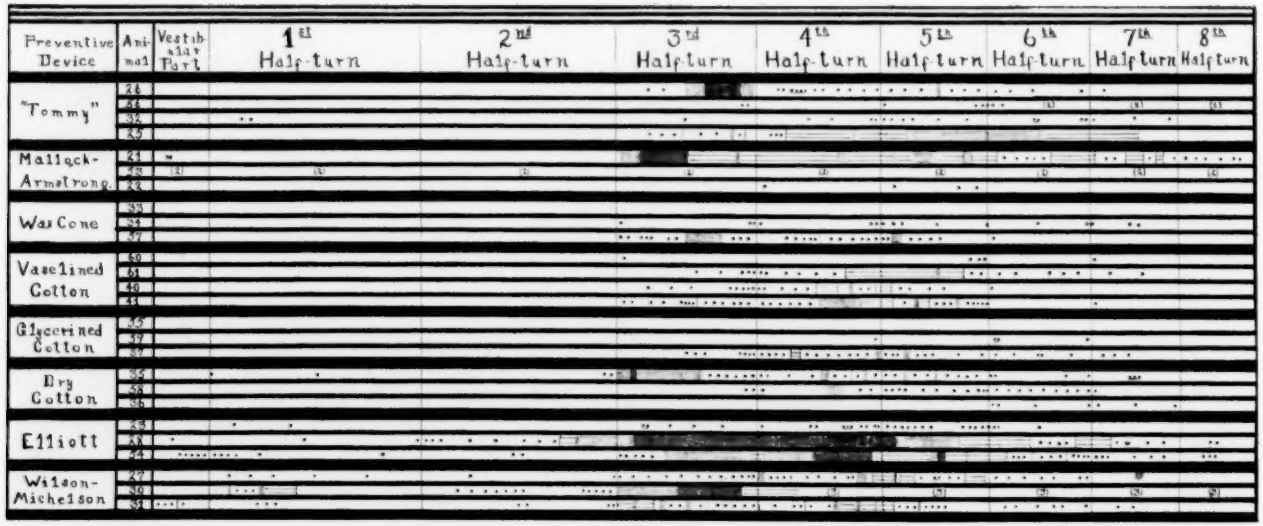


Chart III—Plate IV.

Chart IV—Plate IV.

(For description of charts see page 180.)

Legend for Plate IV

(*See pages* 178 *and* 179.)

For the explanation of the general plan of the charts and of the symbols used, see the text matter, page 159, and the preceding description of lesions. The numbers in parentheses refer to the notes given in the legends for the individual charts.

CHART I.—A graphic presentation of the condition of the organ of Corti in the cochleæ of ears which were entirely open when exposed to the detonation produced by one shot from a 45 caliber Colt automatic pistol, fired with the muzzle at 15 cm., measured from the opposite ear, the barrel pointing downward about 20 degrees from the horizontal from above and in front of the animal along the left side.

CHART II.—A graphic presentation of the condition of the organ of Corti in the cochleæ of the ears which had the open rubber ear and a glass tube, of the dimensions given in the chart for each case, placed in the usual way. With the 2.0 mm. tube, examination of the wax packing after the shooting showed the presence of wax in the end of the tube with animals 47 and 42. (Cf. Table II of the middle ear report.)

CHART III.—A graphic presentation of the condition of the organ of Corti in the cochleæ of the ears which were protected by the methods indicated. These are left cochleæ in every case, and the position of the gun was that given in the legend for Chart I, except that the distance was measured from the protected ear.

(1) (Animal 56) The fixation of these turns is too poor for one to be certain as to possible injuries of limited extent, there are none of large extent.

(2) (Animal 53) The fixation is so poor that the sections are worthless for the determination of detonation injuries.

(3) (Animal 30) The apex of this cochlea was accidentally crushed during its removal; the resulting gross distortion is too great for one to be certain of the condition of the organ of Corti in these apical turns.

CHART IV.—A graphic presentation of the condition of the organ of Corti in the cochleæ of ears which were entirely open when exposed to detonations from a 45 caliber Colt automatic pistol with other than the usual arrangement (see legend to Chart I). The distance from the muzzle and the number of shots fired are indicated in the chart for each case. For the more exact position of the gun each time, reference may be made to Table 1 of the middle ear report.

(1) (Animal 18, right cochlea) The fixation is too poor for one to be certain of more than the general condition; there may be other areas of injury of small extent, but there are no other extensive injured zones.

(2) (Animal 18, left cochlea) This cochlea was not entirely sectioned because of poor decalcification; the areas blocked off are those not sectioned; their condition is accordingly unknown.

PUBLISHER'S NOTE.—The exact distribution of the fourth degree injury does not show clearly in these charts as printed, owing to the lack of differentiation of the intermediate and dark grays.

NOTES ON THE DECOMPOSITION OF ARSPHENAMINE*

By John B. Rieger, M.D., Boston, Mass.

COMMERCIAL arsphenamine is a mixture of dihydroxydiamino-arsenobenzenedihydrochloride, its oxidation products, mineral impurities chiefly sulphur, water, methyl alcohol and ether. Ehrlich and Bertheim[1] in 1912 dried such a mixture in a stream of carbon dioxide at 65°, and on the basis of a combustion ascribed to it the formula $C_{12}H_{14}O_2N_2As_2Cl_2$, $1CH_3OH$, the presence of the methyl alcohol being substantiated by the Mulliken and Scudder test performed on the distillate from an aqueous solution. The formula as now given in the pamphlets accompanying the drug is $C_{12}H_{14}O_2N_2As_2Cl_2$, $2H_2O$. The responsibility for the latter formula can not be stated, although Gaebel[2] as early as 1911, speaks of two molecules of water which are lost when the compound is heated in a current of dry hydrogen at 105°. The present author, having obtained a strong Mulliken and Scudder[3] test on samples of German salvarsan, American salvarsan and diarsenol, attempted a direct determination of the alkoxyl in these preparations, combining for the purpose the Zeisel,[4] Gregor,[5] and Kaufler[6] methods. The sample was dried in a current of washed carbon dioxide for two-hour periods and the alkoxyl simultaneously distilled into hydriodic acid. A pipette bent into a U served as the drying vessel and allowed the sample to be repeatedly mixed by shaking. The results are tabulated.

Brand	Wt. of sample Gm.	Mg. loss in wt.			Mg. alkoxyl, calc. as methoxyl				% loss in wt.
		65°	97°	125°	65°	97°	125°	Dist. Water	
A	0.5976	20.2	13.8	12.4	2.6	0.6	5.5	0.5	7.76
B	1.2094	26.4	20.0	10.0	4.5	3.9	2.0	8.6	4.60
C	1.2034	22.4	30.5	21.7	4.2	3.1	1.0	9.2	6.19

The progressive, though uneven loss of weight from 65° to 125°, argues against the presence of water of crystallization and suggests rather hygroscopic moisture or water of occlusion. The methyl alcohol and ether is probably held in the same way, though there is the additional possibility that part of it is chemically bound to the arsphenamine molecule as ester or ether. Since the distillation of the alkoxyl as given above, is complicated by the formation of halogenated alkyl arsenicals, the figures given can not be strictly accurate, but they show that a considerable part of the loss of weight, formerly calculated as water of crystallization, may be due to alcohol or ether.

THE QUESTION OF ESTERIFICATION

After arsphenamine has been heated for some time at 125° in the manner described, a sublimate of fine colorless needles collects in the portion of the pipette, directly above the surface of the bath, and the fetid alliaceous odor that

*From the Boston State Hospital, Psychopathic Department, Boston, Mass.

is sometimes noticeable when the ampule is first opened, becomes very strong. The crystals are very soluble in water and alcohol, give a white precipitate with silver nitrate, which turns brown and then black, and with iodine and potassium hydroxide they give a strong iodoform reaction. With ferric chloride, the same blood-red color is obtained as given by arsphenamine and o-aminophenol, but when digested with H_2SO_4-HNO_3 and reduced in the Marsh generator, the crystals give no trace of arsenic. The compound is then an ester or ether, possessing an o-amino group, and corresponds with o-anisidine hydrochloride, the crystals of which sublime undecomposed. The fetid alliaceous odor is common to arsines, and in this case seems to arise from a compound soluble in ethyl alcohol, slightly volatile in steam and very slowly reduced to metallic arsenic in the Marsh generator. In these properties it resembles most closely methyl arsenious oxide, $AsCH_3{:}O$. While it is probable that the formation of o-anisidine hydrochloride and of methyl arsine is in this case incidental to the heating process, the potentiality of a like esterification exists wherever arsphenamine, methyl alcohol, and hydrochloric acid are in admixture. During the manufacture of the hydrochloride salt, a great excess of alcohol and acid is present, and through oxidation of either the amino or the arseno group, the acidity of the R.OH is increased and the probability of esterification either during the stage of manufacture or in the ampule, is enhanced. The reactions representing these hypothetical changes are:

1. $[HCl, NH_2.C_6H_3(OH)As{:}]\ 2 + CH_3OH, HCl.$
2. $[HCl, NH_2.C_6H_3(OH).AsCH_3.]\ 2 + CH_3OH, HCl.$
3. $[HCl, NH_2.C_6H_3(OCH_3).AsCH_3.]\ 2 + O_2.$
4. $HCl, NH_2C_6H_3(OCH_3) + AsCH_3{:}O.$

OXIDATION AT THE ARSENO GROUP

The titration of arsphenamine with N/20 iodine solution,[7] is not a direct measure of the arsenic content, but is a measure of the stage of reduction of the arsenic atom, according to the equation:

$$RAs = AsR + 8I + 6H_2O = 2\ RAsH_2O_3 + 8\ HI$$

When arsphenamine is reduced with zinc and hydrochloric acid, the equation becomes:

$$2R\ As\ H_2 + 12I + 6\ H_2O = 2\ R\ As\ H_2O_3 + 12\ HI$$

Hence the percentage of arsenic calculated on this basis will always be lower than that obtained by digestion methods, and the difference must represent the percentage oxidation that the sample has suffered at the arseno group. The reaction is not reversible, as suggested by Gaebel,[8] the endpoint being constant and independent of dilution. Thus diarsenol showed 28.92 per cent arsenic by direct titration, and 30.17 per cent by Lehmann's method;[9] American salvarsan 28.70 per cent by titration and 30.10 per cent by digestion, while German salvarsan showed 29.51 per cent and 30.70 per cent, respectively. Diarsenol was therefore 1.25 per cent oxidized at the arseno group; American salvarsan, 1.40 per cent; and German salvarsan, 1.20 per cent.

OXIDATION AT THE AMINO GROUP

The amount of oxidation at the amino group may be measured by titration with sodium nitrite solution.[10] In the samples of German and American salvarsan and diarsenol examined it was found to be practically nil. In acid solution upon exposure to air there is a slow progressive oxidation to the nitroarylarsinic acid, giving a pink color to the solution. The alkaline solution similarly exposed, and provided that the excess of alkali is not over five molecules, gradually becomes green, probably due to the formation and oxidation of an o-dihydric phenol, ammonia being freed. Arguing from the behavior of pyrocatechol and o-aminophenol, when mixtures of these are exposed to air, one molecule of the dihydric phenol in question then probably rearranges itself with one molecule of the unaltered arsphenamine base, giving upon oxidation a red solution. From this there later separates a dark red-brown precipitate, leaving a colorless supernatant fluid. This precipitate is arseniureted and is probably a phenoxazine derivative, since it is decomposed by alcoholic potash, gives a violet color with concentrated sulphuric acid, is insoluble in water and soluble in concentrated hydrochloric acid to a light red solution.

REDUCTION TO ARSPHENAMINE

Aside from the intrinsic toxicity of the impurities that may occur in commercial arsphenamine there must be considered the relative ease with which these compounds give up their arsenic. The therapeutic utility of organometallic compounds depends upon their inability to ionize, except insofar as the metal may form part of a complex anion. By thus linking the metal to carbon the characteristic oxide action is abolished and the unique effect of the molecule as a whole is obtained. There is evidence that the inability to ionize is not, for all organometallic compounds, an absolute one. Thus, sodium cacodylate, even in fresh solutions, is progressively reduced to metallic arsenic by zinc and hydrochloric acid. Arsphenamine, freshly dissolved, does not ordinarily yield more than a trace of metallic arsenic when reduced in the Marsh generator. Within an hour or two, however, especially if the solution has been alkaline, as much as 5 to 10 per cent of the arsenic may be torn from its carbon anchorage. Using exactly the same weight of zinc and hydrochloric acid, and the same amount of arsphenamine (2 mg.), the reduction is powerfully catalyzed by the solution that has stood an hour or two, whereas the fresh solution has no accelerating affect. Similarly, a zinc-platinum couple placed in a phenoxazine containing solution, brings down a heavy deposit of arsenic, whereas this does not occur in fresh solutions. One is then forced to conclude that the ability to ionize increases, the more oxygen is brought into union with the metal, and that the union of arsenic with methyl, likewise weakens the C-As linking.

REACTIONS WITH COMMERCIAL ARSPHENAMINE

The immediate action of arsenous oxide is to produce a vasoparesis, whereby there results a fall in blood pressure and exudation of fluid. On the heart, it acts like hydrocyanic acid, and according to Schmiedeberg[11] it is only

when injected into the blood stream that it causes paralysis of that organ. The symptoms of subacute and chronic poisoning are more familiar, and upon autopsy resolve themselves into fatty degeneration, chiefly of the heart, liver, and kidney. In this hospital the "nitritoid" reactions have been more numerous, since the employment of arsphenamine of other than German manufacture became necessary. From this it may be argued that the ill effects are not due to arsphenamine itself or to errors in technic, but to preformed degradation products of the base or of its congeners, which either did not exist in the German product or were there present in subliminal amount. The sample of German salvarsan examined was obtained from the Peter Bent Brigham Hospital, and represents a lot purchased since the outbreak of the war. Ormsby and Mitchell[12] state that the later importations of salvarsan were found to be distinctly more toxic than those made before the war, and as considerable doubt has been expressed concerning the source of much of this material, it is impossible to state whether the genuine German salvarsan contained combined methyl alcohol. The presence of the latter is incident to the manufacture of the hydrochloride salt, and the amount would be governed by the age of the sample and the completeness of the drying process. Neoarsphenamine may or may not contain combined methyl, since there is one process[13] of manufacture at least which does not involve the use of methyl alcohol.

PREPARATION OF ARSPHENAMINE SOLUTION

Danysz[14] regards the "nitritoid" reactions as evidence of the precipitation of arsphenamine base into the blood stream. It is true that the monosodium phenolate is precipitated by the carbon dioxide of the air, and the disodium salt is similarly precipitated after a longer time. In other words, carbonic acid is a stronger acid than arsphenamine, and will abstract sodium from the salts of the latter. While blood serum is, in a sense, a bicarbonate solution and contains free carbon dioxide, the circulating blood, if anything, functionates as a weak base. Its hydrogen-ion concentration varies directly as the ratio $H_2CO_3/NaHCO_3$, and the normal value of C_H for the human blood is given as about $10^{-7.45}$, a value that is closely adhered to in health. It is therefore difficult to see how sodium can be abstracted from the monophenolate when the latter is intravenously injected, though this may occur in the test tube. The addition of monophenolate also increases the opalescence of globulin solutions, and this also, in a sense, is a precipitation, though it is not comparable with the milkiness of some sera obtained in life from cases of late vascular degenerative syphilis. It is significant that the "nitritoid" reactions apparently occur more frequently in hospital than in private practice. In the former case the arsphenamine solution is generally made up in quantities sufficient for a dozen or more injections and the alkalized solution is allowed to stand for an hour or two. Some solutions give a garlic-like odor when freshly prepared; others, not until they have stood. This circumstance, together with the size of the dose and the idiosyncrasy of the patient determines whether a reaction will or will not be obtained. Once injected, the occurrence

of subacute or chronic symptoms is determined by the margin that exists or can be made to exist between the elimination of the drug and its reduction by the tissues.

SUMMARY

Commercial arsphenamine may contain an arseniureted methyl compound, which decomposes either in the ampule or in solution, with liberation of arsenous oxide or a cacodyl-like substance. Some preparations betray the presence of the arsine by their garlic-like odor when dissolved; others develop it only after having stood in solution for hours. According to the amount that may have accumulated, the dosage and the idiosyncrasy of the patient, a reaction marked by fall in blood pressure, dyspnea and cyanosis may occur. Once the drug has been injected, the occurrence of subacute or chronic arsenic poisoning is determined by the margin that exists or may be made to exist between its elimination and its reduction by the tissues. There is evidence that this reduction to metallic arsenic occurs too readily for safety with present commercial preparations of arsphenamine.

The work was prematurely terminated because of conditions brought on by the war, and the results are therefore not conclusive. The preparation of a neoarsphenamine without the use of methyl alcohol and a study of its therapeutic behavior would do much to prove or disprove the hypotheses advanced.
I am deeply grateful to Dr. Lawson G. Lowrey, of this hospital, for his valuable cooperation in the work.

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THE ROLE OF TUBERCULOSIS IN DEMENTIA PRECOX*

(Preliminary Study)

By H. I. Gosline, M.D., Worcester, Mass.

THE relations of the numerous forms of tuberculosis of the various organs which have proved themselves so valuable a study both from the standpoint of public health and from that of the research specialist have received little if any attention from psychiatrists since the time of Kahlbaum in 1873 (September). At the meeting of the Massachusetts Medical Society, June, 1916, it was stated in the Section on Tuberculosis that insanity, especially dementia precox, was one of the predisposing causes of tuberculosis. This was the opinion of Kahlbaum, held many years ago with regard to catatonia. At that time he pointed out, without laying any special stress upon them, the symptoms clinically known as those accompanying tuberculosis such as sweats, drowsiness, and loss of weight. He mentioned headache, and at times the bowels show diarrhea or are costive. Despite Kahlbaum's dominant interest in the intracranial findings, we find him saying that tuberculosis occurred in five of the seven cases which came to autopsy, making a percentage of 71.3. Not only has there been no advance over Kahlbaum's time in the discovery of the relationship between tuberculosis and dementia precox, but we have made little if any advance in our separation of paresis from dementia precox, in cases that are mentally on the border line. Even now, in spite of the added advantages of the Wassermann technic on blood and spinal fluid, we frequently find cases coming to autopsy with the diagnosis of dementia precox which clinically showed neurologic evidence of syphilis of the central nervous system and which at autopsy show granulations in the fourth ventricle or other incriminating evidence. As for the confusion of alcoholic cases with dementia precox we have made no advance whatever. As a matter of fact, we have turned the other way and there is a tendency today to consider alcohol as an incident in dementia precox rather than as a possible cause of the clinical picture.

With regard to the relation of tuberculosis to dementia precox, Kraepelin has made a real advance perhaps in considering that the confinement of the patient is a predisposing cause to tuberculosis rather than the tension or passive resistance of the muscles of the thorax, which was Kahlbaum's idea of the patient's predisposition to tuberculosis.

It is the purpose of the following study to establish somewhat more definitely from a statistical point of view, the relation which apparently exists between tuberculosis and dementia precox. The percentage of dementia precox cases resulting in death from tuberculosis is somewhat higher than Kahlbaum's figures when studied over a slightly longer series, and it is possible that Kahlbaum's percentage would have been somewhat larger if careful pains had been

*From the Laboratory of the Worcester State Hospital, Worcester, Mass.

Publisher's Note.—The second report of this series will appear in an early issue.

taken to rule out those cases which had an alcoholic history or which gave evidence clinically or pathologically of having suffered from syphilis.

Ruling out these cases together with those which possibly were suffering with some other infection at the time of onset of their psychosis, we have a percentage in thirty cases of 73.3 who died of tuberculosis. The percentage of dementia precox cases affected with tuberculosis should be higher than the figures show by considering merely death in dementia precox. In a great majority of the remaining percentage we will find a history of tuberculosis paralleling or antedating the history of the mental disease. The reason for the present low percentage is the obvious one, our lack of clinical methods for the discovery and early diagnosis of that most puzzling of diseases, tuberculosis. Even with the modern development of the roentgen ray in the diagnosis of pulmonary cases and with our added knowledge of the early clinical signs, our clinical methods are admittedly deficient. We no longer expect to find the tubercle bacillus in the sputum, urine or feces in order to make our diagnosis, and yet we know that many cases pass through the hands of competent physicians without recognition. Anatomically, the condition is just as difficult of accurate diagnosis. It is well known that there is difficulty in distinguishing tuberculosis from syphilis microscopically or macroscopically. The diagnosis, then, is not infrequently made wrongly, not only before death but after death. On the mental side the picture is even more confusing. We know that alcoholics may give the picture of dementia precox and that general paretics may appear like catatonics at times. Various infections may be accompanied by catatonic symptoms. There is no way from the mental picture to distinguish the cause of the disease. It is doubtless true that many more errors creep into mental diagnosis than into ordinary physical diagnosis.

Though death from dementia precox is a small matter, disability from dementia precox is a large matter. Upon the disabling factor in dementia precox rests a fair part of the necessity for large institutions for the care of the insane. In certain parts, between 75 and 90 per cent of the permanent population of these hospitals is made up of patients who have suffered from dementia precox and who are mentally incapable of carrying on an independent existence any longer.

The present study is based upon 108 cases which have come to autopsy since the institution of a permanent laboratory in this Hospital. This number is practically 8 per cent of the total number of autopsies performed in that period. The cases were thoroughly reviewed by the writer and all those discarded which gave a history of alcohol, syphilis, or infectious disease coming on at the onset of mental signs, or which gave anatomic evidence of syphilis, or which mentally might be classed under any other category than dementia precox, or in which there was some doubt as to the diagnosis in the minds of certain members of the staff. So treated, there were 63 cases of the 108 that could be promptly discarded. Tuberculosis, as a cause of death, necessarily could not save them. The one criterion as to whether they should be retained was that they should be undoubted cases of dementia precox. Fifteen cases showed special features which put them outside the pale of frank dementia precox because there might be a possibility of discussion pro and con. This left a total of 30 cases which

were retained as a basis for this study. Of this number 21 died of tuberculosis of various organs, chiefly of the lungs. One died of pulmonary abscesses from which tubercle bacilli were discovered in the smear. These 22 cases thus make a percentage of 73.3 dying of tuberculosis.

That one may have an adequate basis of knowledge of the way in which the cases were selected, a short review of the discarded cases will be attempted first. Table I is a list of discarded cases.*

TABLE I

CASE NO.	CAUSE OF DEATH	REMARKS
III-9	Retention of urine.	Granulations of IVth ventricle.
III-37	Cerebral hemorrhage.	No hallucinations or delusions.
IV-21	Edema of lungs.	Patient had fits (?).
IV-25	Lobar pneumonia. Pulmonary embolus.	Question of imbecile.
IV-37	Pulmonary tuberculosis.	Patient had fits (?).
IV-42	Pulmonary tuberculosis.	Granulations of IVth ventricle (?).
V-35	Apoplexy.	Hemorrhage at 40 years. Body tissues not examined.
V-42	Pulmonary tuberculosis.	No delusions or hallucinations (?). Patient and father alcoholic.
VI-30	Pulmonary tuberculosis.	(?) Idiot or juvenile paretic.
VI-40	Bronchopneumonia.	(?) Toxic-infection-exhaustion. Pneumonia, nephritis, diphtheria, and bronchopneumonia.
VI-41	Acute peritonitis.	(?) Idiocy. Seizures at 65 years. Old tuberculosis, intestinal ulcers (tuberculosis or cancer?).
VI-62	Enterocolitis. Vegetative endocarditis.	(?) Infection-exhaustion. Acute onset at 54 (10 to 20 days), (?) nephritis, old tuberculosis.
VII-1	Pulmonary tuberculosis, enterocolitis.	Alcohol and polyuria.
VII-9	Pulmonary, intestinal, laryngeal tuberculosis.	Maniacal, prostitute, alcohol (?), lues (?).
VIII-15	Suicide by hanging.	Psychopath (?), manic depressive (?), hysteriform tantrums, freudian complex (?), fits at 7 or 8. Old tuberculosis, cystic ovaries.
IX-2	Bronchopneumonia.	"Chronic mania" (?), manic depressive, tantrums, suggestible. Pulmonary tuberculosis.
IX-19	Acute miliary tuberculosis. (First called sarcoma bronchial glands.)	Syphilis with secondaries. Absent k. j., pupils stiff to accommodation, (?). Babinski; no hallucinations.
IX-31	Heart failure.	No hallucinations or delusions, three attacks. Rales, markedly costive. Old pleurisy.
IX-82	Pulmonary and intestinal tuberculosis.	Two attacks. (?) history of lues. One child, one miscarriage.
X-9	Tuberculous enteritis.	(?) Imbecile. Moderate alcohol. Old tuberculosis.
X-10	"Cardiac incompensation."	Suicidal. Fear affect. Old tuberculosis.
X-20	Dermoid cyst with carcinoma (hemorrhage).	Fear affect. Some alcohol.
X-49	Heart disease.	No delusions. Autopsy incomplete.
X-76	Heart failure.	Onset at 63. "Depressive delirium." (?) Presenile. Old pleurisy.
XI-15	Sarcoma of jaw.	(?) Alcohol and syphilis. Pulmonary tuberculosis.

*The question of mistaken diagnosis does not enter here. These cases were not suitable for this study for reasons which will be apparent.

TABLE I—(CONTINUED)

CASE NO.	CAUSE OF DEATH	REMARKS
XI-25	Duodenal perforation and peritonitis.	Patient claims delirium tremens.
XI-30	Uremic convulsions.	No history. "Hysteriform seizures." Admits exposure. Neurologic signs.
XI-44	Pernicious anemia.	(?) Freudian. 1st husband luetic? Operation "erosion of womb" (?), pulmonary tuberculosis. Pleural effusion.
XI-52	Basilar meningitis.	Onset at 50. Alcohol. "Crazy after men." "Faints." Clinical t. b. Previous typhus.
XIII-4	Broncho- and lobar pneumonia.	Autopsy incomplete.
XIV-17	Acute pulmonary edema. (Cardiac dilatation.)	(?) Epileptic imbecile. 9 attacks. 1. Acute mania following grippe. 2. Secondary dementia. 3. Recurrent melancholia. 4. Recurrent melancholia (manic). Alcoholic.
XIV-42	Acute dilatation of heart. Acute hemorrhagic pancreatitis.	(?) Infection. Acute mania. Convulsions.
XV-6	Ruptured heart.	Incomplete history. Tuberculosis at apex.
XV-22	General peritonitis.	"Tubes reddened." Acute, following tonsillitis. Apical scars, double plastic pleurisy.
XV-50	Chronic colitis.	Onset at 42. (?) Manic depressive, atypical. Old pleurisy. Pupils unequal, postmortem.
XV-58	Acute colitis.	"Fantastic paranoia." "Paranoid condition" (?) Imbecile. Followed injury. Alcoholic.
XV-67	Acute colitis.	No past history.
XV-74	Exhaustion.	Autopsy incomplete.
XV-79	Gangrene. Cellulitis.	(?) Manic depressive. (?) Paresis. Admits exposure. Alcohol. K. j. and pupils unequal. Granulations, IVth ventricle. Old tuberculosis.
XV-84	Pulmonary and intestinal tuberculosis.	Alcohol. (?) Lues.
XVI-37	Chronic valvular endocarditis. Anasarca.	Immoral. Glands enlarged. Alcohol. K. j. diminished.
XVII-4	Miliary tuberculosis.	No history. No notes 1902-1911.
XVII-16	Multiple abscesses.	Syphilis. Alcohol.
XVII-25	Chronic nephritis (pyelo-). Edema of lungs.	(?) Constitutional inferior. Some "drink."
XVII-40	Abdominal carcinosis.	(?) Constitutional inferior. No delusions or hallucinations. Alcohol. Admits exposure. Old pleurisy.
XVII-74	Bronchopneumonia.	(?) Paranoid condition in constitutional inferior. (?) Syphilis. Old pleurisy.
13-3	Lobar pneumonia.	(?) Constitutional inferior. No hallucinations. Onset at menopause at 42. Apical scars.
13-10	Aneurysmal dilation of heart. Pulmonary infarct and edema.	(?) Syphilitic paranoid condition. Moderate alcohol. Granulations IVth ventricle.
13-31	Acute pancreatitis (?). Fat necrosis. Cholelithiasis.	Onset at 40. (?) Septic or tuberculosis temperature.
13-35	Cardiac aneurysm. Coronary sclerosis.	(?) Infection-Exhaustion. Adhesive pericarditis. Apical scars.
13-40	Septic decubiti. Abscess of lung. Vegetative endocarditis.	"Coincident with muscular rheumatism." Onset at 52.
13-46	Acute enteritis. Early peritonitis.	Syphilis with secondaries.
14-8	Decubiti. Septicemia (?).	Tuberculosis temperature. Absent knee jerks. Some pleural adhesions. Sclerosis of posterior columns.
14-21	Suicide by hanging.	(?) Psychopath with manic depressive. Pulmonary tuberculosis.

TABLE I—(CONTINUED)

CASE NO.	CAUSE OF DEATH	REMARKS
14-27	Postoperative plastic peritonitis. Carcinoma sigmoid with intestinal obstruction.	(?) Defective. Old pleurisy.
1915.6	Pulmonary tuberculosis.	(?) Cerebrospinal syphilis. Blood positive, spinal fluid doubtful. Tuberculosis in sputum.
1915.21	Bronchopneumonia. Pellagra.	(?) Defective. W. R. Blood doubtful, then negative. Gumma of liver (?). Apical scar.
1915.29	Bronchopneumonia.	One faint. (?) Prostitute. Old pleurisy and "latent" tuberculosis.
1915.40	Acute hemorrhagic pancreatitis. Sclerosis and constriction left coronary with thrombus.	Alcohol.
1915.45	Pellagra.	Alcohol. (?) Lues. Wife had miscarriages.
1916.29	Lobar pneumonia. Parenchymatous nephritis.	Onset at 53. No hallucinations. Old pleurisy.
1916.30	Carcinoma sigmoid and rectum.	(?) Toxic-exhaustion.
1916.32	Catalepsy.	Temperature. Influenza in sputum and blood (taken at autopsy).

A brief summary will reveal certain clinical and certain pathologic data on which these cases are dismissed. Of the clinical reasons are the fact of absence of hallucinations or delusions in certain cases, the presence of convulsive seizures, the question of imbecility, constitutional inferiority, psychopathic personality, manic depressive insanity, alcoholic psychosis, syphilitic history or other evidence of syphilis, or the presence of certain other factors of a toxic, infectious, or exhaustive nature. On the pathologic side the factors are granulations of the IVth ventricle, cerebral hemorrhage at the age of forty, adhesive pericarditis, and question of gumma of the liver. A few cases had incomplete records.

It will be noted that there is frequently a history of tuberculosis in these patients and some died of the disease but this has not been used as a reason for retaining cases.

Table II is a list of the cases retained.

TABLE II

CASE NO.	CAUSE OF DEATH	REMARKS
II-31	Deglutition pneumonia	Pleural cavities obliterated. Left upper lobe, radiating scar and bronchiectatic cavities.
III-6	Gangrene of lungs.	(?) Tuberculous. Old tubercles at apex.
III-14	Pulmonary tuberculosis.	
III-24	Pulmonary tuberculosis.	
III-31	Pulmonary tuberculosis.	
III-43	Pulmonary tuberculosis.	Tuberculosis of liver and kidneys.
IV-8	Pulmonary tuberculosis.	
IV-16	Pulmonary tuberculosis.	
IV-18	Pulmonary tuberculosis.	
IV-47	Tuberculosis of lungs, liver, kidneys, spleen.	
V-3	Pulmonary tuberculosis (tuberculous pneumonia).	
V-39	Pneumonia.	Clinically and anatomically tuberculosis.

TABLE II—(CONTINUED)

CASE NO.	CAUSE OF DEATH	REMARKS
VI-33	Cancer of duodenum.	Liver affected. Death at 31. Clinically tuberculosis and anatomically tuberculosis of lungs. Father and mother died of tuberculosis.
VII-25	Endocarditis.	Old tuberculosis anatomically.
VII-41	Pulmonary tuberculosis.	Hemorrhages. (?) Tubercles of pia.
VII-46	Pulmonary and intestinal tuberculosis.	Positive sputum. Albumin and casts.
VIII-3	Pulmonary tuberculosis.	
X-21	Bronchopneumonia.	(?) Old tuberculosis.
XII-28	Tuberculosis and mitral insufficiency.	Acute course of 10 days' duration.
XIII-17	Pulmonary tuberculosis.	Rapid course.
XVI-22	Lobar pneumonia (pneumococcus meningitis).	Old pleurisy and pulmonary tuberculosis.
XVI-23	Pulmonary tuberculosis.	
XVII-43	Tuberculous intestinal ulcers. Acute degenerative nephritis.	Old pulmonary tuberculosis. "Frontal encephalitis."
XVII-57	Typhoid fever. Gangrenous cellulitis, pelvis.	Old pleurisy. Apical scars.
14-7	Abscesses of lung.	Smear from abscess positive for tuberculosis.
1915.18	Pulmonary and intestinal tuberculosis. Acute vegetative endocarditis.	
1915.25	Fibroid phthisis. Chronic interstitial nephritis.	
1916.25	Tuberculosis, ileum, etc.	Solitary tubercle brain and cerebellum.
1916.36	Double lobar pneumonia.	Old pleurisy.
1916.37	Chronic interstitial myocarditis.	Old pleurisy. (?) Tubercle of spleen.

Certain of these cases show a remarkably intimate connection between the course of their physical disease, tuberculosis, and the course of their psychic disturbance. This type of case has been described by Claude and Rose[1] and by them has been considered in the group of Toxic-Infection Psychoses. The number of cases in the present study which resemble that of the French writers is seventeen. These will receive special attention in a separate study. It is fitting that they should be considered in the present group of dementia precox cases until such time as they shall receive proper recognition as belonging to the toxic-infectious group.

Doubtless the dementia precox group will in the future be further split up on the physical side, as the start has already been made in splitting off paresis and those cases of an infectious origin. But the psychic complex can never be split into anything but its psychologic elements or possibly, its psychopathologic elements. It must not be forgotten that cases of paresis which appear like dementia precox are, on the psychic side, really dementia precox, though the physical cause is the process caused by the spirochete. It is already admitted that alcoholic cases of a certain type may simulate paresis, as the time-honored name alcoholic pseudoparesis bears witness. The necessary basis for the similar pictures is not the causative agent, but is the location of the pathologic process.

The ideas outlined above with regard to paresis and alcoholic pseudoparesis may apparently be applied also to dementia precox and may prove to be of more than passing significance. The work of Southard[2] on the relation which

exists anatomically between the catatonic form of dementia precox and parietal lobe lesions and between the paranoid form and frontal lobe lesions, independently of the causative or accompanying physical factors, furnishes us the necessary anatomic substrate.

The time-worn question as to why all cases affected with our supposed causative agent do not give us the mental disease has no longer any logical value since the discovery of the cause of paresis. It is now recognized that this is another question in quite a different field and need not concern us here.

The question next arises as to the reasons for considering tuberculosis as a causative factor in the cases upon which this study is based. It has already been said that seventeen cases showed the mental disease to be so nearly parallel to the physical that they will be given separate consideration with a similar case published in the French literature. It will suffice here to give the age of onset, age at admission, and age at death in these cases and to describe more at length the other thirteen cases whose course did not parallel so succinctly the physical disease.

In Table III are given seventeen cases with age at onset, etc.

TABLE III

CASE NO.	AGE AT ONSET	AGE AT ADMISSION	AGE AT DEATH
III-6,	46	47	48
III-14	18	21	23
III-24	31	31	32
III-31	39	39	40
III-43	25	25	27
IV-8	19	19	20
IV-16	26	27	28
IV-18	22	22	23
V-3	23	24	25
VII-41	24	24	27
VIII-3	44	45	45
XII-28	19	20	20
XIII-17	18	18	19
XVI-23	25	29	29
XVII-43	33	34	34
14-7	28	28	29
1916.25	24	26	29

The striking thing in this series as it stands is the short duration from onset to exit. Another incident of interest is the predominance of the third decade cases, the decade from twenty to thirty. It seems that we may at some future time be able to split off such cases from the total group of dementia precox in some such way as that suggested in the article by the French writers mentioned above.

Comparing this table with the causes of death mentioned in Table II, we find that all but one died of tuberculosis and the cause of death in that one (Case III-6, gangrene of lungs) may be suspected to be in some way linked with tuberculosis since there were tubercles at the apex. One case (XII-28) was complicated by mitral insufficiency. Two had tuberculosis of other organs than the lungs as cause of death (XVII-43, 1916.25) and one died of abscesses of

the lungs in the smear of which tubercle bacilli were found. These few facts will serve in a rough way to indicate the close connection with tuberculosis which exists in these cases.

Let us next approach those cases in which the connection is not so clear cut. In these cases the ages at onset and at admission are frequently separated and perhaps more frequently the ages at admission and at death are far apart. These are the mild cases which stay in the community until the relatives can no longer care for them or the cases which enter the hospitals with an acute attack of mental trouble from which they recover but with residuals which incapacitate them for further independent existence in the community.

The age at onset, etc., in these cases is given in Table IV.

TABLE IV

CASE NO.	AGE AT ONSET	AGE AT ADMISSION	AGE AT DEATH
II-31	33	43	76
IV-47	29	60	61
V-39	25	32	74
VI-33	26	26	31
VII-25	22 (?)	35	53
VII-46	27	27	34
X-21	22	22	23
XVI-22	29	30	50
XVII-57	25	26	29
1915.18	44 (?)	45 & 49	57
1915.25	(?)—"Years"	48	49
1916.36	25	27 & 31	54
1916.37	28	31	65

Comparing Table II, the causes of death will be found to be varied, as they would be expected to be in recovered cases. They are pneumonia (II-31, V-39, X-21, XVI-22, 1916.36), tuberculosis (IV-47, VII-46, 1915.18, 1915.25), cancer of the duodenum (VI-33), cardiac disease (VII-25, 1916.37), and typhoid fever (XVII-57). But in all these cases there was clinical evidence in the feeling of weakness on the part of the patient, or the variations in weight, or in the temperature chart, or at autopsy there was anatomic evidence of the presence of tuberculosis, or of its previous existence. This evidence, linked with the course of the mental symptoms in these cases, gives a view of the relationship which is as clear as any which can be obtained by present-day methods short of the actual demonstration of organisms or of their products in cases such as this paper has outlined. That such demonstration of organisms and their products may now be possible is a matter for the future. Certainly the method of Petroff[3] for the cultivation of the tubercle bacillus from body tissues and the complement-fixation test as practiced by Bronfenbrenner and others[4] for tuberculosis should be tried in these selected cases. It is not to be hoped or expected that such tests and examinations will show any high percentage of positives in random or routine examinations of dementia precox cases. This on the theory that dementia precox is a mental symptom-complex which depends for its existence upon the difference in function of brain areas which are topographically distinct. The cases selected must be those of tuberculosis, if the tests are to be positive. That there is a certain residue of dementia precox

CASE II-31*

PHYSICAL	MENTAL	SUMMARY
1878-'79 — Abnormal appetite with vomiting begins and continues till the end.	1864—Insane 10 years. Excited, violent, shy, suspicious, then seclusive. 1865—"Disinclined to exertion." 1868—Violent at times. 1871—Nervous and excitable. 1876—"Can remember things done in a former existence," seclusive. 1879-'79—More sociable. "Catholic priest comes into his room at night and makes him vomit." Writes much incoherently. 1881—"Visions." Talks to self. 1884—Visions of the dead. Noisy at night. 1886—Denies having relatives. 1887—Bothered by devils and spirits. 1888—Undresses in daytime. Prescribes for imaginary patients. "Imps fly into room and drop arsenic into food." 1889—Talks, laughs and sings to self in room. "Prussic acid put through window by enemies." 1891—Put meat and water in bottle and took "vile mixture." Goes out after refusing for five years. Says he is a ghost murdered 30 years ago. 1894—Disoriented.	Insane 10 years. Active on admission. Thirteen years, dull with active periods. Then deluded. Two years later, abnormal appetite and vomiting which continued. Three years later, visual hallucinations. Progressively more active with more profound disintegration of the personality. Autopsy reveals distended ileum and large redundant colon. Old pleurisy and pulmonary tuberculosis. Fresh bronchiectatic cavities. Chronic nephritis. Vessels atheromatous.

*In the Conduct Charts: × means that the sign was present every day or nearly every day of the month. ± means that the sign occurred many times during the month. | means that the sign occurred but once during the month.

cases in the causation of which tuberculosis plays a part, is the theme of this paper.

The cases are presented in chart form as being the easiest way in which to correlate mental and physical events.

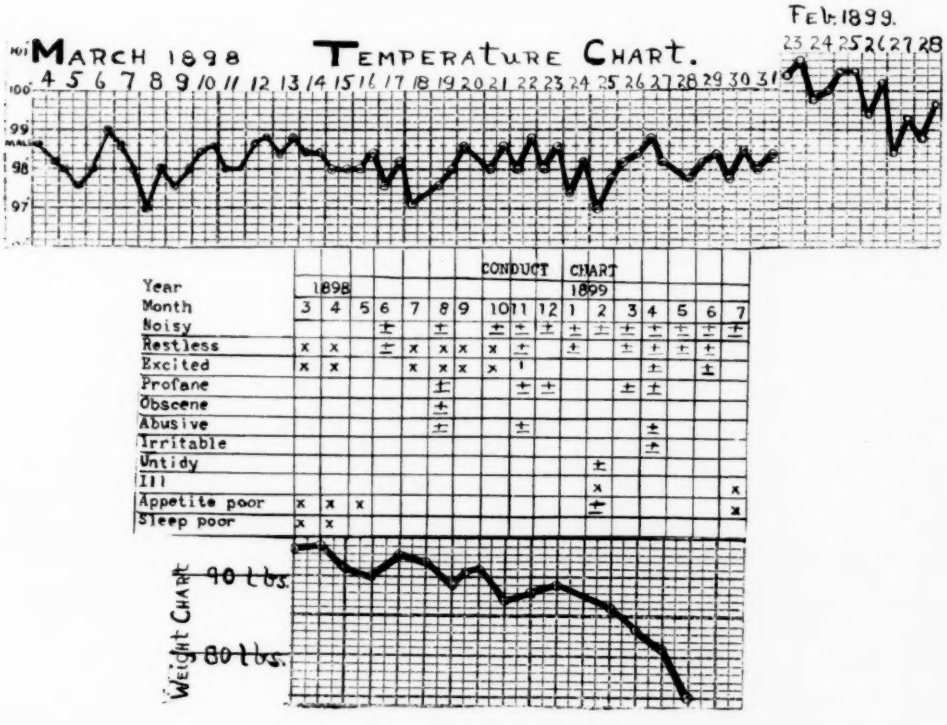
CASE II-31.—It is obviously impossible to judge the age of old adhesions or of quiescent tuberculous processes and hence impossible to assume any connection between those old processes found in this case and the mental history extending back over twenty-eight years. No one will deny that the connection is possible since we know that a tuberculous process may be latent or subacute for many years, but many will think that the connection is unlikely. Perhaps the active lighting up of the mental process in the last three years of life will be allowed to be in some way dependent upon the process which led to the formation of the fresh bronchiectatic cavities found at autopsy.

CASE IV-47.—This case is similar to the above in the long duration and character of the disease, lasting thirty years with active episodes and finally running a terminal course of activity. At autopsy there were active and latent tuberculosis with tubercles in the liver, kidneys and spleen. With the late active course there was weakness, downward tendency of the weight, and unexplained temperatures which were suggestive of tuberculosis in places.

CASE V-39.—A history of exposure to tuberculosis is followed by active mental symptoms which soon lead to dementia while on the physical side there is chronic bronchitis with asthma. A morning and afternoon temperature kept for two years gives fair evidence of the tuberculous nature of the patient's physical

CASE IV-47

PHYSICAL	MENTAL	SUMMARY
March, 1898 — Numerous, depressed, nonpigmented scars in skin. Reflexes exaggerated. Tremor of hands and tongue. Urine negative. "Feels weak." April, 1898—Insomnia. Feb., 1899 — Temperature, lungs negative. Untidy. March, 1899—"Has a cold." June, 1899—Sits with feet in chair and hands on head. July, 1899—Lungs negative. Albumin present in urine. July 20 (next day), slight dullness at left base, posteriorly. Diarrhea. Too weak to walk. Temperature 97.8° to 102.2°, pulse 75 to 134, respiration 19 to 42. July 22, 1899—Died.	1866—Onset with delusions of losing property. Collected old tin cans, etc., into her room. Talkative. Woke nights, screaming. Careless. 1866-1898 — Gradual silliness, childishness, "temper" by breaking dishes. Muttering, 1888-1898. 1897—Wandered away and said her folks were dead. 1898—Went to a stranger's house and ordered them out. Let herself out of window with rope at midnight, ordered stranger out of his house again and hid in his orchard. Disoriented for time, place, person. Says she is 23 years old. Irrelevant, obscene, silly, disconnected speech. Auditory hallucinations. Abusive, profane, restless, excited, noisy, violent. Cries and tries to escape. Irritable and seclusive. 1899—Resistive. April—Aggressive.	Onset at 29 with delusions and active episodes, gradually becoming feeble-minded over the next thirty years. At 60 conduct and speech become active and remain so till death at 61. Physically there is great "weakness," insomnia, unexplained temperature and a "cold." Autopsy shows apical adhesions. Nodules in right and left lungs, some encapsulated and hard, some with soft, caseous centers. The liver is "peppered" with small gray-white spots. Nodules in kidneys and spleen. CASE IV-16



CASE V-39

PHYSICAL	MENTAL	SUMMARY
Husband died of tuberculosis. 1879—Pain in chest when heart is weak. Feet swollen. Chronic bronchitis. Chronic gastroduodenal catarrh with jaundice. 1887 — Chronic bronchial trouble. Acute exacerbation later. 1892—Remains in bed. Asthma. 1897, Oct. 29—Habit scoliosis, emaciated, diminished expansion, dull right base posteriorly and crackling rales. Apices hyperresonant. Knee-jerks diminished. Dec. 3—Dullness right anterior. Breathing rough left and bronchial right. 1898, June 2—Sputum negative for tuberculosis.	At 25, after childbirth, excited, threatening, restless, jealous, religious. 1858—Boston Lunatic Hospital. Mania with delusions. 1879 — Worcester State Hospital. Demented. 1885 — Discharged, unimproved. 1887 — Admitted, melancholy. Notices attentions of nurses later. 1892—Fails to notice attentions. 1896—Groans when spoken to. 1898—Quiet. Says "many thanks" for each attention of the nurse.	History of exposure to tuberculosis. Active onset at 25 and at admission, age 32. Demented at 53 and showing chronic bronchial trouble which is called asthma at 66. Lung signs and dementia increase till death at 74. Autopsy shows distended cecum and rest of colon shrunken. Adhesions over right upper lobe externally and posteriorly and lower lobe externally, posteriorly and to diaphragm. Lower one-half of right lower lobe solid, blue-gray, and studded with gray nodules. Scars at apex of left lung and inferior part of lower lobe solid, bluish and nodular.

Year	1897	1898												1899												1900			
Month	12	1	2	3	4	5	6	7	8	9	10	11	12	1	2	3	4	5	6	7	8	9	10	11	12	1	2	3	4
Untidy	x	x	x																										
Ill	x	x	x		x	x	x	x	x		x	x	x	x	x	xx		x	x	x	x	x	x	x	x	x	x	x	x
Appetite poor	x	x			x	x	x	x	x		±	x	x	x	x	x	x			±	x	x	x	x		x	x		
Sleep poor							x									±	±	±	x	x	x	±	x	x					

No weight chart—patient too weak. (See Temperature Charts, pages 197 and 198.)

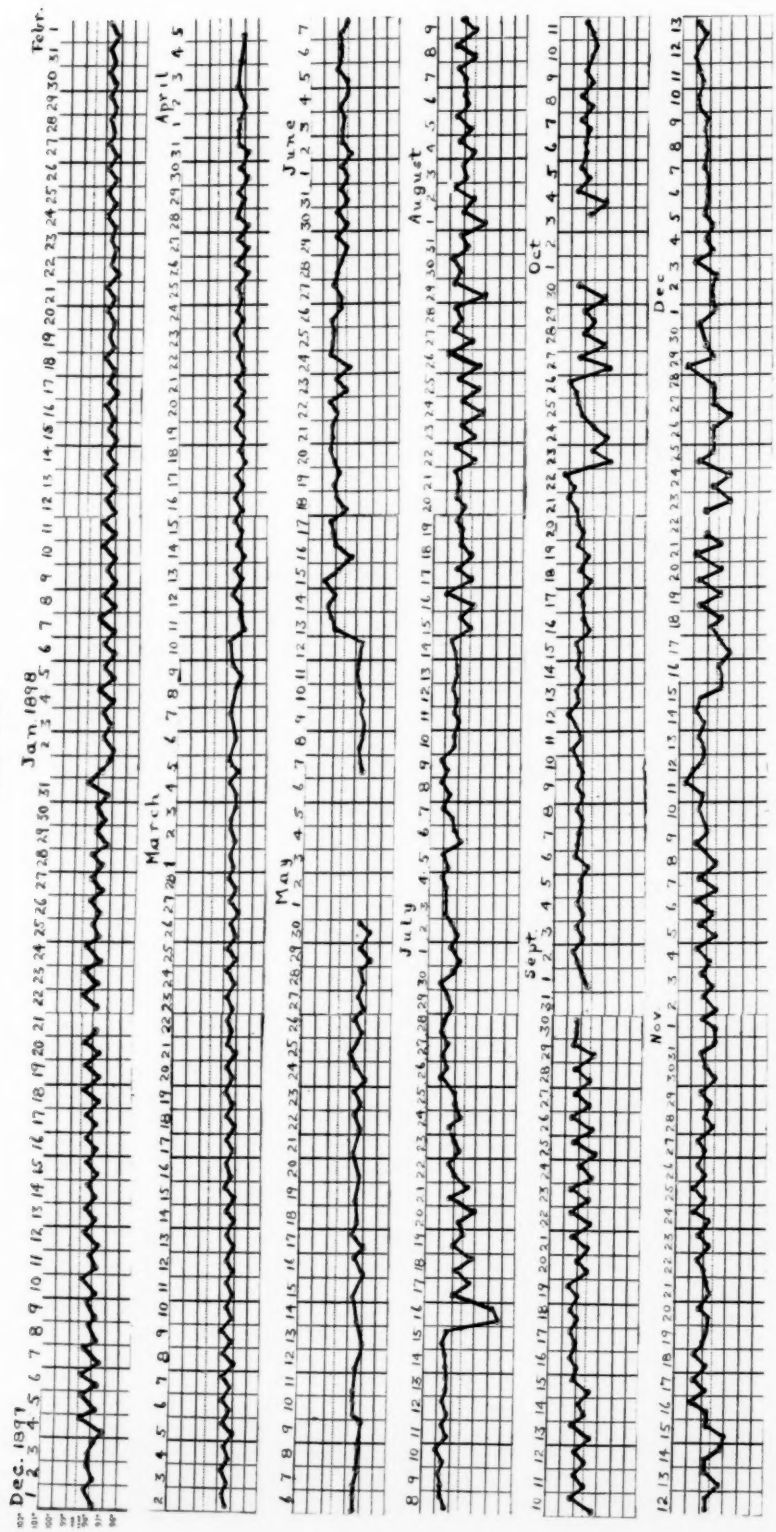
trouble. Autopsy confirms the suspicion with signs of chronic and of terminal acute tuberculosis.

CASE VI-33.—Exposure to tuberculosis is followed by mental symptoms and physical signs such as a feeling of exhaustion, anemia and poor state of nutrition. Patient dies following hemorrhage from an ulcer of the duodenum thought to be cancerous. Death at thirty-one. There were old pleurisy and nodules in the lungs, difficult to differentiate the nodules as tuberculosis or as cancerous metastases. The shape of the chest suggests pleurisy, or even an old empyema or plain effusion. The weight chart suggests an independent, metabolic disorder (but not of endocrine origin) and this parallels the noisiness and restlessness of the patient. The temperature chart sufficiently explains the nature of the patient's weakness and the total case casts doubt upon the cancerous nature of the duodenal lesion.

CASE VII-25.—Sudden onset with slow course extending over thirty years and showing two distinct active episodes. Terminal nephritis but without mental reaction. Old pleurisy and pulmonary tuberculosis. Absence of active tuberculous lesions. Following last active period a remarkable increase in weight during which mental signs were subsident.

CASE VII-46.—Sudden onset with active symptoms which continue with slight change till the end. Duration seven years. No physical notes till sixth

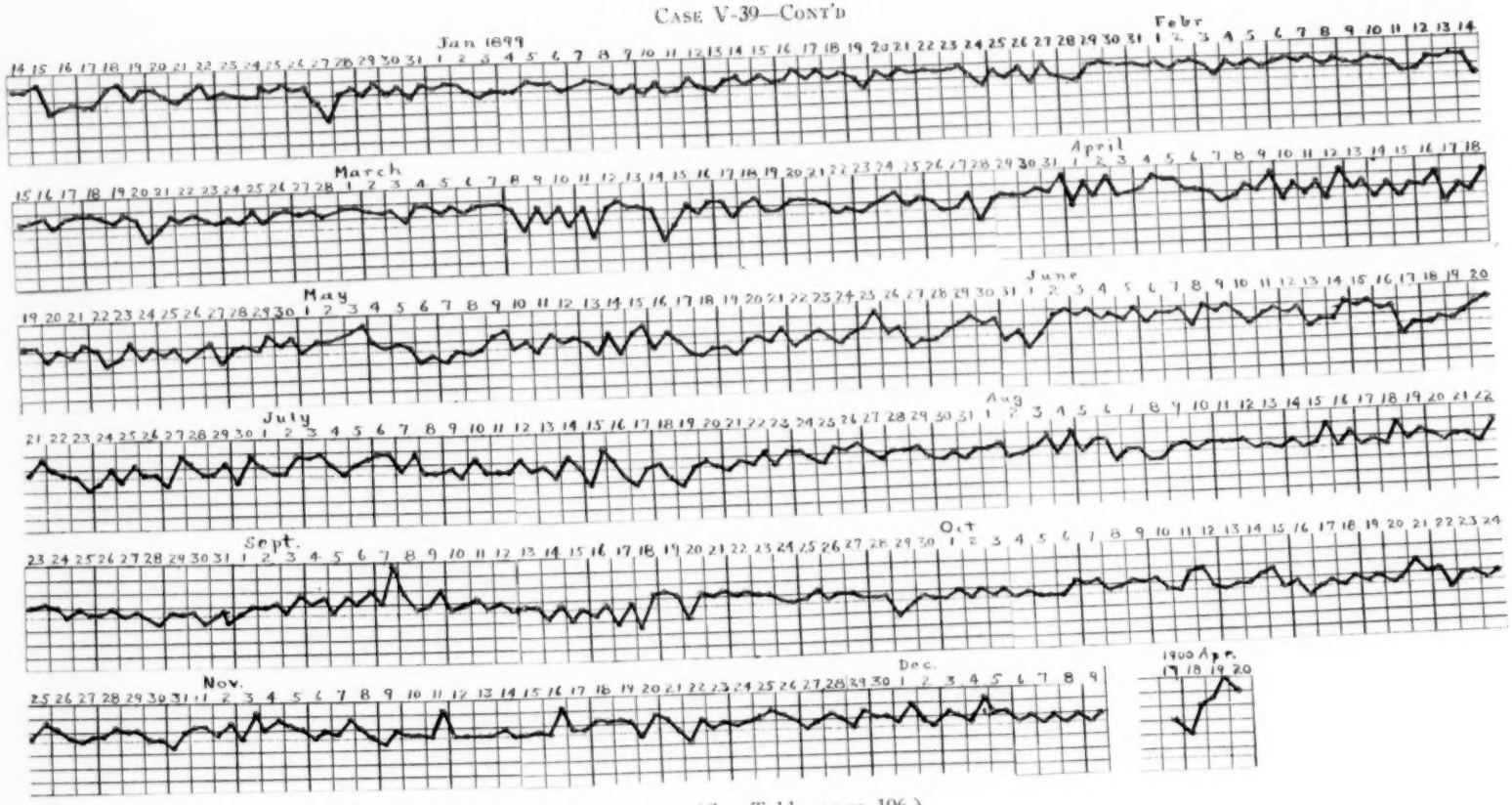
CASE V-39



(See Table, page 196.)

(Chart continued on page 198.)

CASE V-39—CONT'D



(See Table, page 196.)

year when weight falls, a typical temperature is noted, and the mental activities on the conduct side increase. Autopsy showed old pleurisy, pus cavities and tubercles in the lungs, tuberculous ulcers of the ileum and cecum, and free fluid in the chest and abdominal cavities.

CASE X-21.—A sudden onset with active physical and mental symptoms ends in death in one year. This case resembles the French case in the main but lacks so positive proof of the presence of tuberculosis. At autopsy there were abundant pleural adhesions. There was atheroma of the aorta. Changes of this nature in the arteries are frequent even in early cases of dementia precox.

CASE XVI-22.—An active onset of short duration is followed by fourteen years of comparative inactivity and six years without active mental symptoms. The weight shows no general upward or downward tendencies though there are occasional transient variations. Autopsy shows extensive, old pleurisy and an encapsulated, caseous mass with several tubercles in relation to an old apical scar. The history of the last six years is rather inadequate, but it would seem that the encapsulated mass should have some effect on the organism unless the amount of absorption from it were very small. The slight variations in weight, mentioned above, show a fairly close connection with disturbed periods. One might imagine that there was some connection between these periods of weight loss and mental disturbance and the periodic poisoning of the organism by some hidden focus, but it would be asking too much to expect one to believe it.

CASE XVII-57.—Acute onset with mild, active symptoms and headache is shortly followed by weakness and tuberculous temperature. Death in three years with symptoms unabated. Weight seems independent of mental state. Tuberculosis of the lungs completes a picture very similar to the French case but not included there because death was due to typhoid.

CASE 1915.18.—Gradual onset with remissions. Weak from the beginning. The weight drops, then the appetite fails. A moderate afternoon rise in temperature accompanies the fall in weight. Variations in temperature regularly accompany the changes in conduct, the refusal to work and the loss of appetite. It is to be regretted that the weight chart is incomplete. Pulmonary signs develop long after the weight and temperature charts are practically pathognomonic. Autopsy reveals pleurisy, tuberculous pulmonary abscesses, and tuberculous ulcers of the ileum.

CASE 1915.25.—A mild course of many years terminating with active symptoms of one year's duration. Weight drops, temperature is suggestive. Lungs give evidence of tuberculous process of long duration with old pleurisy and final tuberculous pneumonia.

CASE 1916.36.—Onset gradual, symptoms constant but of low grade for many years. Pleural adhesions of moderate extent. Though the weight dropped somewhat and the temperature is slightly suggestive, the physical picture is incomplete on the whole. The symptoms were mild corresponding to the slight changes at autopsy. The patient's homicidal attempt was apparently due to the content of his hallucinations rather than to his own heightened activities.

CASE 1916.37.—A long, chronic mental disease ends with vascular trouble.

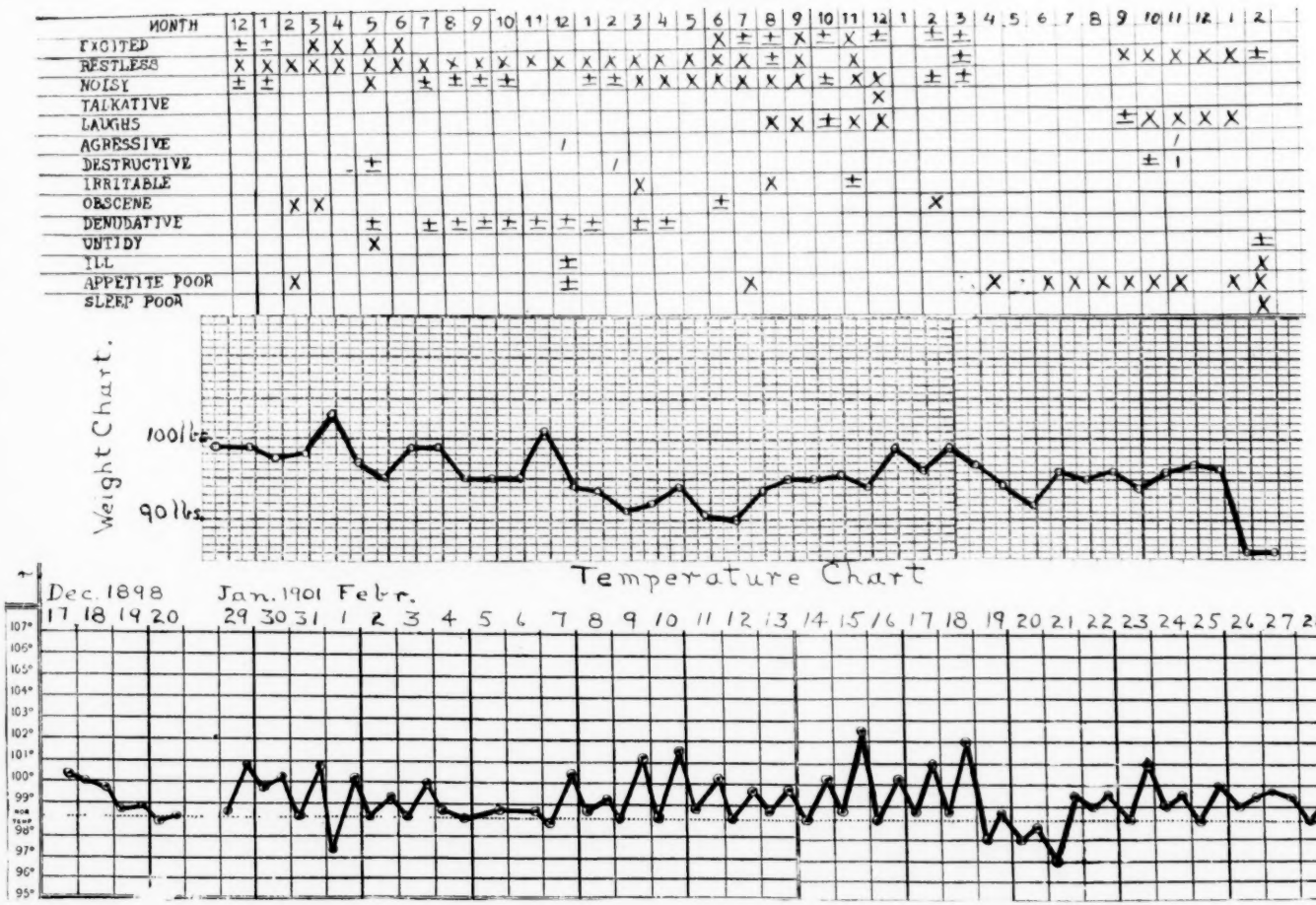
CASE VI-33

PHYSICAL	MENTAL	SUMMARY
Father died of tuberculosis at 30. Mother died of hemorrhage of the lungs when young. 1896, May-June — Had a "nervous shock," i. e., grew dizzy, faint, shivered and was cold, then felt exhausted and weak. Summer—Complained of headache much. On visit gained appetite and flesh. December — Insomnia and poor appetite. P. E.—Poorly nourished, skin anemic, feels tired, headache all over and in her eyes, knee jerks slightly exaggerated. Right chest, low, is prominent, and posteriorly projects forward. Left chest small anteriorly, depressed below, prominent posteriorly. Scoliosis, lower dorsal, to left and upper compensatory to right. Right base dull. Periods irregular. 1901, January—In bed, no complaint but weakness. (See temperature chart.) February—Fainted when getting out of bed. Ten hours later, passed liquid blood and clots by rectum. Reds, 1,512,000. Whites, 35,700. Hb., 15%. Later, tumor in right upper quadrant. Sputum negative for tuberculosis.	1896, December — Dull, depressed, immodest, staring. Thought she did things mechanically without "feeling" what she was doing. Admitted—confused, hallucinated (auditory), disoriented for time and place, recent and remote memory good, talkative, "food and medicine" poisoned, suspicious, "people in her room." 1897, January—"Food tastes strangely." April — Theatrical and constrained in her movements. Fails to recognize friends. Kisses everyone. May—Rhyming. June—Exhilarated, silly. November—Dances and kicks. 1898, July—"Electricity in the air works on her nerves and makes her dance." Appearance careless. 1899, June—Strikes stomach and head with fist, pulls her own hair. 1900, May—Untidy in every way.	Sudden onset with physical symptoms at 26. Mental signs 6 months later. Exposed to tuberculosis. Signs in lungs and shape of chest. Mental signs more active for three years. One year later, exhaustion, profound anemia and death at 31. Autopsy—Hair tinged with gray. Transverse colon at pubes. Duodenum a hard, nodular mass with soft areas; attached to kidney, to hepatic flexure by old, dense adhesions, and to gall bladder. Adhesions right lung, externally, left lung, posteriorly except apex and to diaphragm. Right middle lobe contains soft, flat, solid bodies from which a milky, thick juice may be scraped. Nodules in surface and substance of liver, whitish milky, thick fluid and "cheesy" plugs. Center of one completely "cheesy." Second part of duodenum seat of deep ulcer. Edges thick, dense, pork-like; walls pale gray. Tissue necrotic with many fibrous strands. Necrotic material yellow-gray. Right kidney cystic, calculi. Calcified plaques in pia.

(See Chart, page 201.)

CASE VI-33

Conduct Chart



(See Table, page 200.)

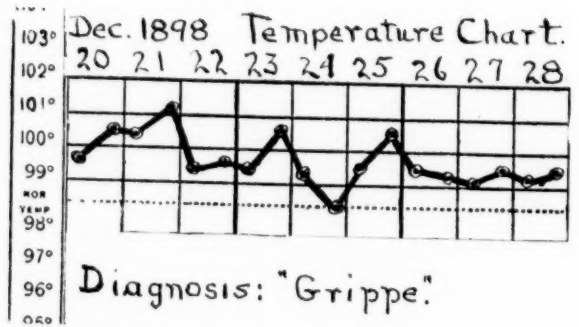
CASE VII-25

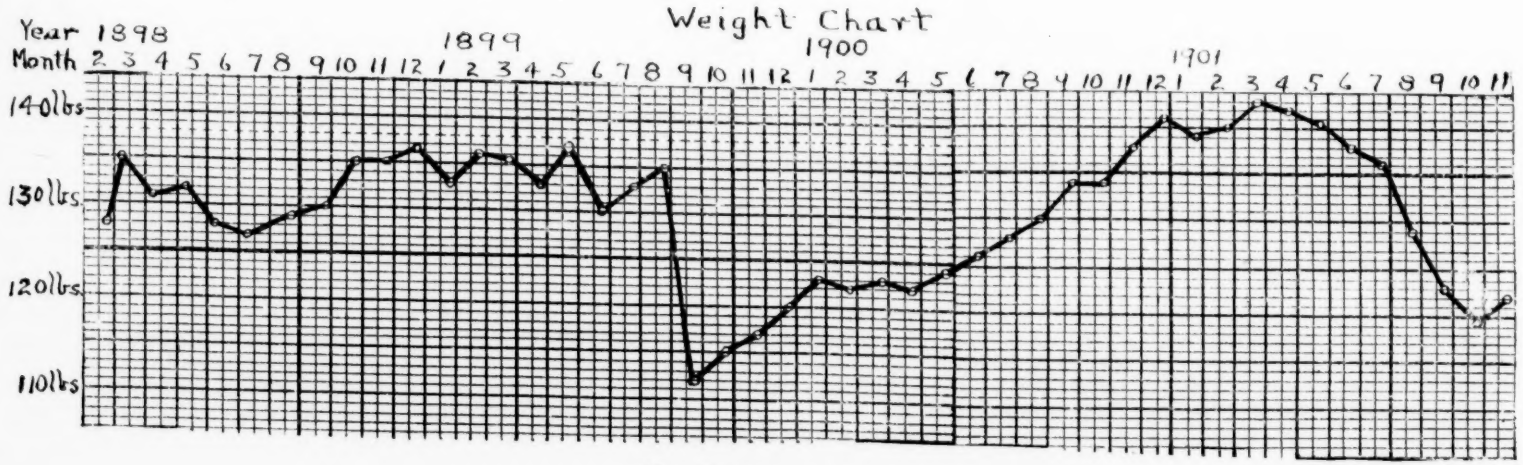
PHYSICAL	MENTAL	SUMMARY
1898, Dec.—"Grippe." 1901, Dec. 14—Considerable albumin, numerous granular and few epithelial casts. Dec. 21—Albumin moderate, epithelial, hyaline and granular casts. Dec. 26—No albumin, few epithelial, many hyaline and granular casts. Leucocytes, 8,500. Chill before temperature but malaria not in blood. Dec.-Jan., '01-'02 — Four hourly "septic chart."	1870 (?)—Shortly after marriage, jumped out of window and ran into swamp. 1884—Admission. "A ring regulates her mind." Food poisoned. Things filled with electricity. Snakes in her bed. Conversation disconnected. Talks to self. More excited during menses. 1887—Incoherent. 1889—Sits about, picking face. 1895—Face sore from picking. 1896—Talks to self. 1898—"Fleas bite her," so she picks. Assumes attitudes and stares. 1899—Scolds, laughs, talks. Does not want to be observed—talks rapidly, without noticing question, when addressed. 1901—Never converses; answers monosyllabic. Feb., 1898—Denudative 2 days. April, 1898—Noisy 1 day.	Sudden onset at about 22. After 13 years, admitted with delusions, incoherency. Self-mutilation after 5 years. Ten years later, active episodes. Two years later, dull, demented, signs of nephritis. Death. Autopsy—Omentum adherent, right iliac fossa. Adhesions right apex and over left lung posteriorly, to pericardium and to diaphragm. Right lung—thick, puckered pleura at apex with hard, irregular, non-caseated nodule. Small nodules in middle lobe. Left lower lobe nodular. Infarct of spleen. Horseshoe kidneys.

(See Chart, page 203.)

CONDUCT CHART

YEAR	1898	1901	1902
MONTH	AUG.	DEC.	JAN.
NOISY	±		
IRRITABLE	±		
OBSCENE	±		
PROFANE	±		
UNTIDY	±		X
APPETITE POOR	±	X	X
ILL		X	X





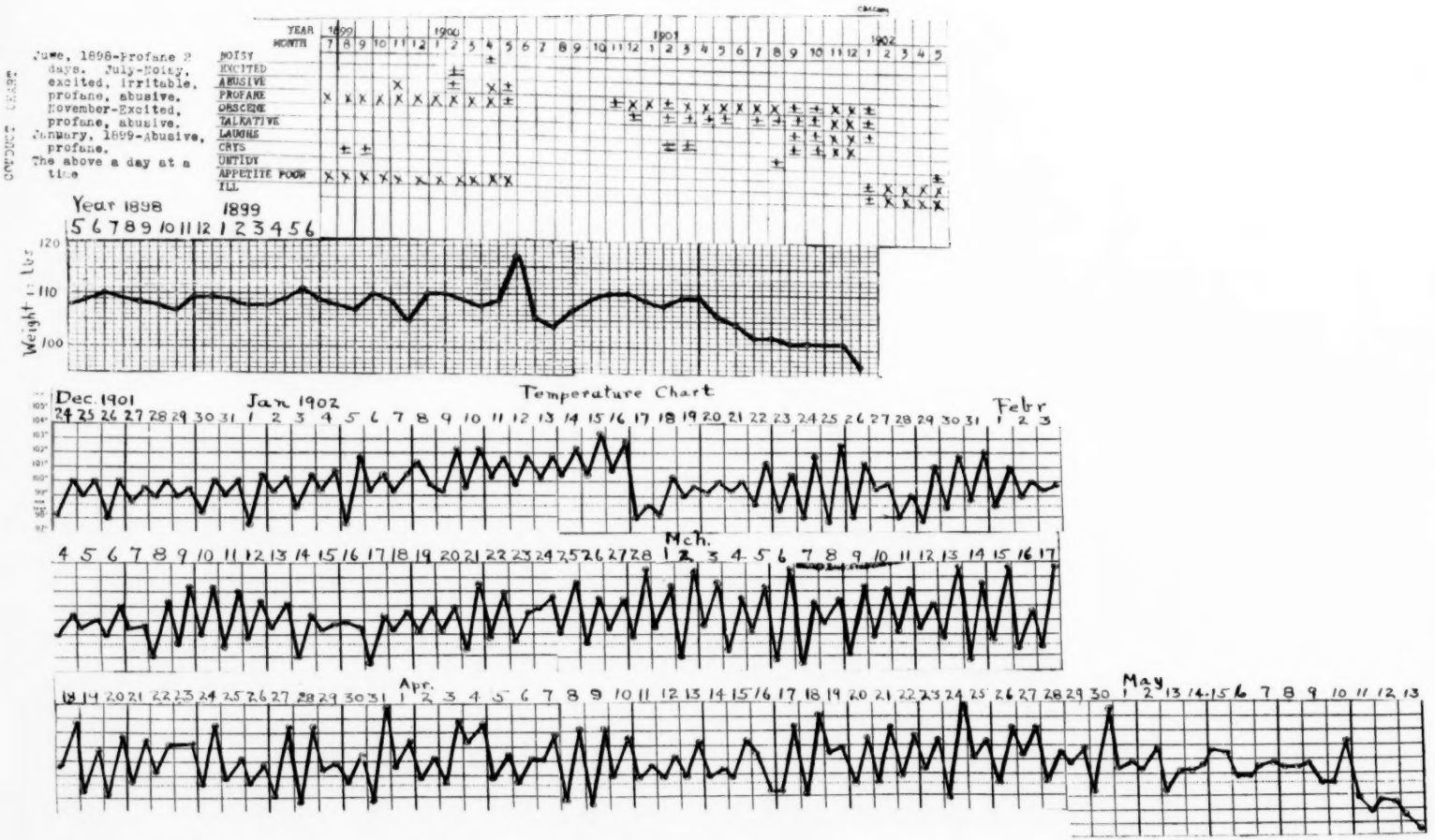
(See Table, page 202.)

CASE VII-46

PHYSICAL	MENTAL	SUMMARY
	1895—Threatens husband and mother-in-law. Profane and vulgar to unseen people. Irritable, laughs and talks to self. Unusual libido et potentia.	Sudden onset at 27 with delusions of a sexual nature and with hyperkinetic signs. One year later, demented. Next three years, periods of activity, gradually losing memory, etc. In sixth year of the disease, signs of pulmonary tuberculosis. Death at 34, one year later.
	1896—Demented.	
	1898—Aggressive, irritable, abusive, profane. Sex delusions about husband and his mother. Works, attends entertainments, does fancy work.	Autopsy—Fluid in abdomen. Right upper lobe anteriorly adherent, externally and posteriorly throughout and to diaphragm. Left adherent externally and posteriorly throughout and to diaphragm. Free fluid in chest.
	1899—Oriented for time and place. Careless appearance. March—Will not work. July—Agreeable and helpful. Aug.-Oct.—Profane.	Right lung, nodular. Bean to hickory-nut size cavities with pus in upper lobe. Gray, white elevated nodules in lower lobe. Left lung nodular; interlobar adhesions. Small, pus cavities in upper lobe and large, empty cavity in lower lobe. Ileum—2 meters above cecum, healed ulcers 2x3 cm., raised, white edges and dark gray bases. Lower is transverse constriction with gray base. Ulcers cecum.
1901, Dec.—Right apex dull front and back. Anemic.	1901—Laughs several months.	
1902, Jan.—Dull first and second space and posteriorly to second spine. Breath sounds harsh. Rales. Large amount of albumin, few epithelial casts. Feb.—Tuberculosis in sputum. Considerable albumin, granular and epithelial casts. Apr.—Spits blood.	1902—Thinks here four years.	

(See Chart, page 205.)

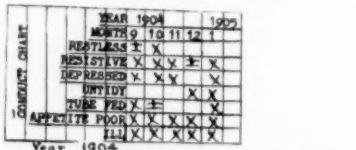
CASE VII-46

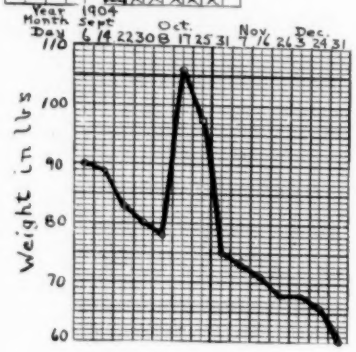


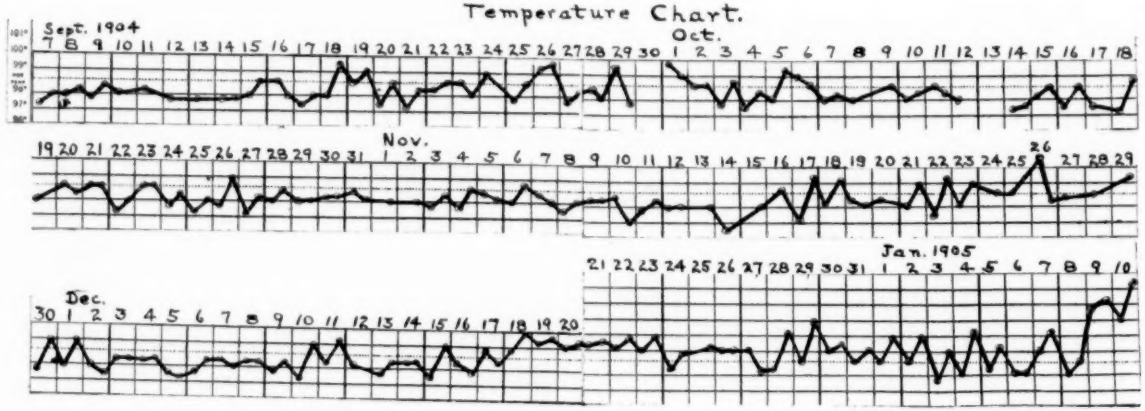
(See Table, page 204.)

CASE X-21

PHYSICAL	MENTAL	SUMMARY
1904, Jan.-Sept.—Headache, loss of appetite and weight, insomnia, feeble. On admission—reflexes brisk. Rare hyaline cast.	1904, Jan.-Sept.—Afraid she is going to die. Mute, confused, hallucinated (auditory). Tried to bite mother. Ran about house till exhausted, then tried to jump from window. Complains of taste of food. Admitted in September, mistakes identities. Resistive, untidy, vermin. Dazed expression. Disoriented. Recent memory poor. Sept. 30—Restless, facial expression stolid, mute. Spoon fed. Oct.—Tube fed. Diarrhea. 1905, Jan.—Untidy. Spoke to nurse and hoped to get well.	Sudden onset at *22* with active physical and mental symptoms. Admitted in dazed condition. Death at *23* in demented condition. Autopsy—Adhesions right lung anteriorly and to diaphragm, left lung upper lobe, posteriorly. Atheroma of aorta. Aortic valves calcified at bases.

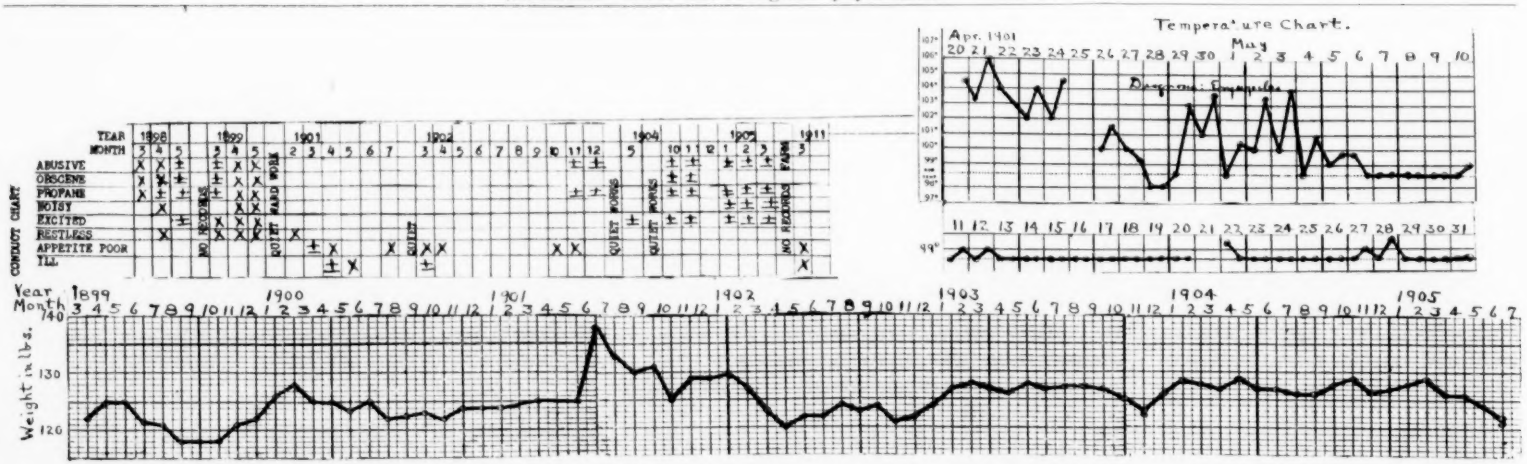






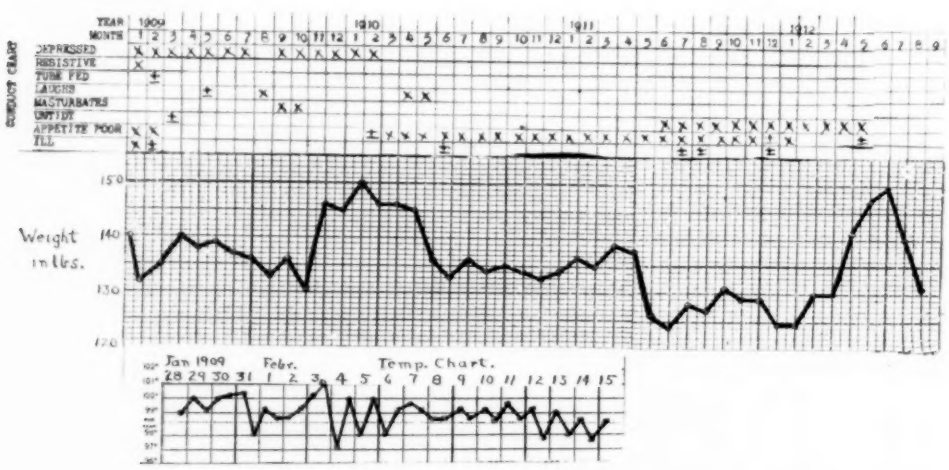
CASE XVI-22

PHYSICAL	MENTAL	SUMMARY
Grandmother and brother suicides. 1901—Erysipelas. Diminished breathing right with increased vocal fremitus. "Limbs are stiff." (See temperature chart.) 1905-1911—Worked at farm. March 19—Pneumonia. March 25—Death.	1890—Nervous, ideas of persecution, aggressive, violent. 1891—Irritable, abusive. "His voice is carried everywhere in the building." 1892—Demented. 1894—Abusive, vulgar, irritable, changed his name. 1896—Excited if called by correct name. 1898—Profane, active. 1899—People here have hands, feet, and heads cut off and wear his clothes. 1901—Threatens homicide. Disoriented. No insight. "Building a throne, he is king, patients are all convicts." 1902—Irritable, expansive. 1903—Abusive. Works. 1904—"Silent conversation" (auditory hallucinations). 1905—Disoriented, time and place. No hallucinations. Does not recognize physicians.	Active onset at 29. Admitted at 30. Next 14 years dementia broken by active periods with hallucinations and delusions. Next 6 years dull, mentally inactive, working. Autopsy—Right pleural cavity obliterated, left shows adhesions at apex. Right apex large, irregular, sunken, stellate scar. At base, cordlike mass of encapsulated, yellow, caseous material. Other nodules in relation to cicatrix. Pneumonia and pneumococcus meningitis.



CASE XVII-57

PHYSICAL	MENTAL	SUMMARY
Paternal grandmother insane. 1908—Headache. 1909, Jan.—Tremor of tongue and hands. Urine negative. Feb.—Says he is weak. (See temperature chart.) 1912—Typhoid, positive Widal. Exitus.	1908—Irritable, worried, sat gazing into space. Thought family against him. Said to have chased women and to have exposed himself. Threatened homicide. Confused, seems stupid. 1909, Jan.—Suspicious, laughter explosive, apprehensive, ideas of reference, somatic and sexual ideas, word salad, depressed, resistive. Admitted. Feb.—Hesitant. "Would like to freeze up dead." Tube fed. Oct.—Light work. Reticent. Masturbates and exposes self. Resistive. Whispers under breath. 1911—Silly, grins, repeats questions, dull, disoriented.	Onset at 25 with mild, active symptoms. Admitted less than a year later. Rapid course of three years with catatonic features. Death from typhoid. Autopsy—Adhesions right lung, diaphragm and base. Apical, puckered scars each apex. Ulcers ileum.



There are pleural and peritoneal adhesions and pulmonary emphysema. A tuberculous nodule appears in the kidney.

The thirty cases selected, then, show something more convincing as to the connection between them and tuberculosis than the mere incidence of death from tuberculosis. Seventeen cases, to be described later, or 56.6 per cent show a connection so apparent that they are considered to belong to the toxic-infectious group by some. Thirteen cases considered here show a course which may in a fairly definite way be considered to be bound up with a clinical or anatomic tuberculosis. Tuberculosis was demonstrated anatomically in all of them and the anatomic picture was the one to be expected from the course of the mental picture, the physical signs, such as weight and the subjective symptoms, and from the temperature chart.

SUMMARY

There is a definite group of cases of dementia precox in which tuberculosis may be considered to be a causative factor and, possibly, the causative factor.

Of such a group, 73.3 per cent die of tuberculosis. In 56.6 per cent the courses of the mental and the physical disease run parallel and in the other 43.3 per cent, which is the percentage which recover and die of a later tuberculosis or of some other cause, a previous or concurrent tuberculosis is demonstrable.

Special complement-fixation tests on the blood and spinal fluid and special cultural methods applied to such cases should yield a high percentage of positive results and give us an added advantage in early diagnosis.

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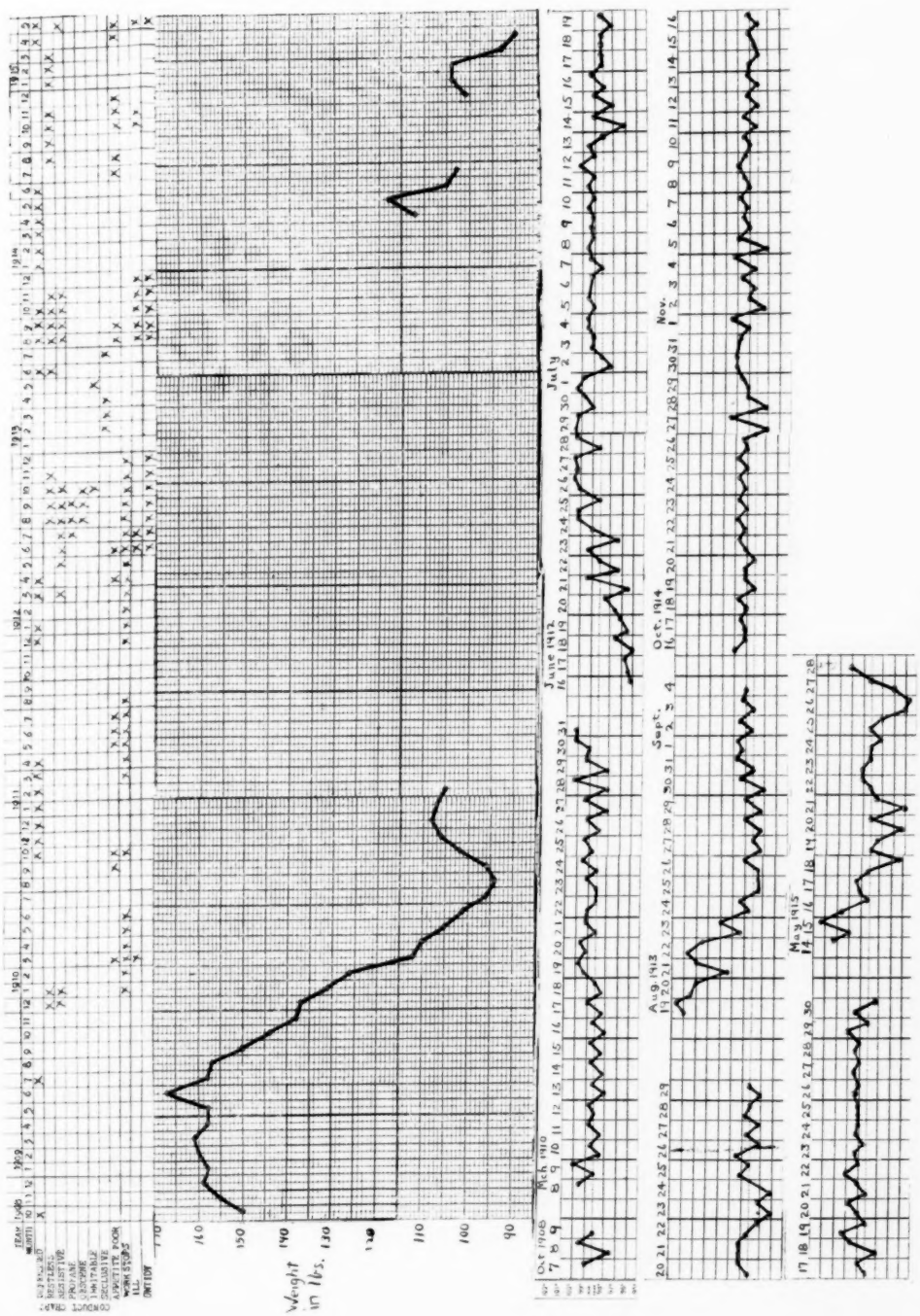
[4]Bronfenbrenner, J., Kahn, Morris, H., Rockman, J., Kahn, Max: Further Studies of Biological Methods for the Diagnosis of Tuberculosis, Arch. Int. Med., 1916, xvii, p. 492.

CASE 1915.18

PHYSICAL	MENTAL	SUMMARY
	1902—Ideas of reference, auditory hallucinations, ideas of persecution. Went to the roof to escape voices. Depressed. No insight.	Onset gradual and with remissions at 44 (?). Symptoms improve with hospital residence, grow worse outside and with gradual dementia of moderate degree. Weakness from beginning. Finally signs of pulmonary trouble.
1903—Had a "numbness in her fingers." Reflexes exaggerated. Appetite poor.	1903—Admitted to McLean Hospital—depressed and hallucinated at times. Released but later returned. "Priest made faces at her," voices dictated orders which she obeyed. Suspicious and seclusive. Incoherent. Transferred to Worcester.	Autopsy—Adhesions right upper lobe, posteriorly; both lungs to diaphragm. Fluid, left chest. Right lung, cavity at apex, tubercles in lower lobe. Left lung, surface nodules in upper lobe, coalescing tubercles forming abscess cavities in lower lobe and subpleural hemorrhage. Irregular, circular ulcers ileum near cecum.
1904—Has stomach trouble and feels tired, calls it dyspepsia.	1904—Discharged. Went to church every day, troubled by "martial law."	
1908—Is very tired. Appetite good. Sleeps well. Hair dyed.	1908—Returned. Excited. "Went to church to get rid of treason." Laughs and mumbles. Memory good. Oriented. "Voices defame her character." Reticent. No insight.	
	1909—Seclusive, intractable at times.	
1911—Albumin present, hyaline, waxy, granular casts, edema of ankles, diarrhea.	1911—Memory impaired, reticent, ideas of reference and persecution.	
1913—Dysentery. Trace albumin, few red cells.	1914—Unoccupied, seldom speaks, dull. Disoriented, memory poor, deluded.	
1914—Feet bother her. She is tired. Albumin, s. p. t. Emaciated. Sounds rough at apices. Wassermann, blood, negative. October—"dysentery."		
1915—Cough, sputum negative. Sounds harsh, rales. Red cells, 4,216,000. White cells, 35,440. Hb. 75%. Exitus.	1915—Apathetic.	

(See Chart, page 211.)

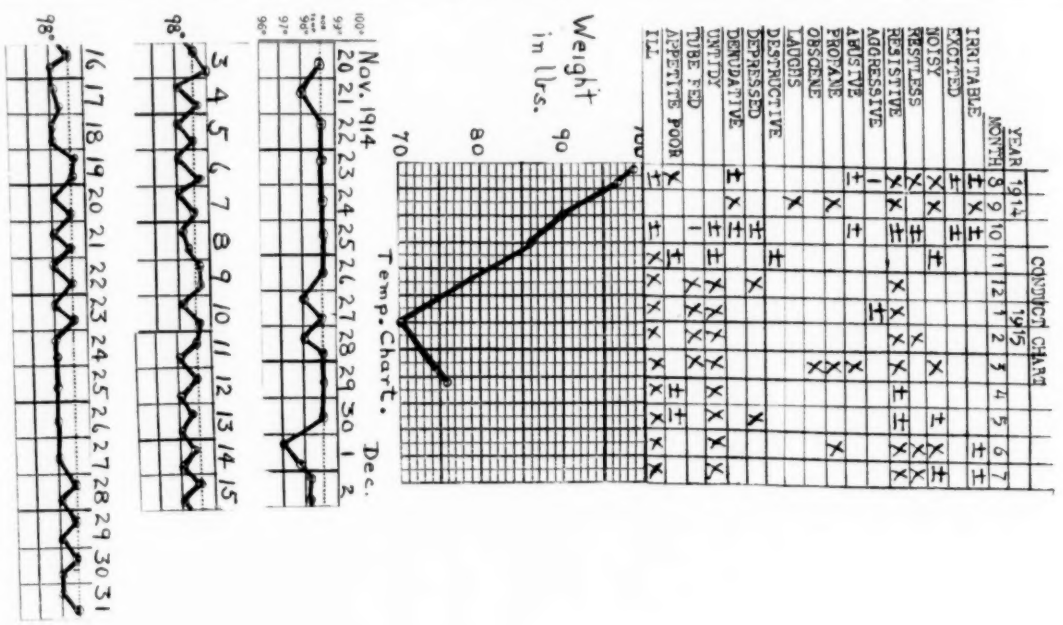


CASE 1915.18

(See Table, page 210.)

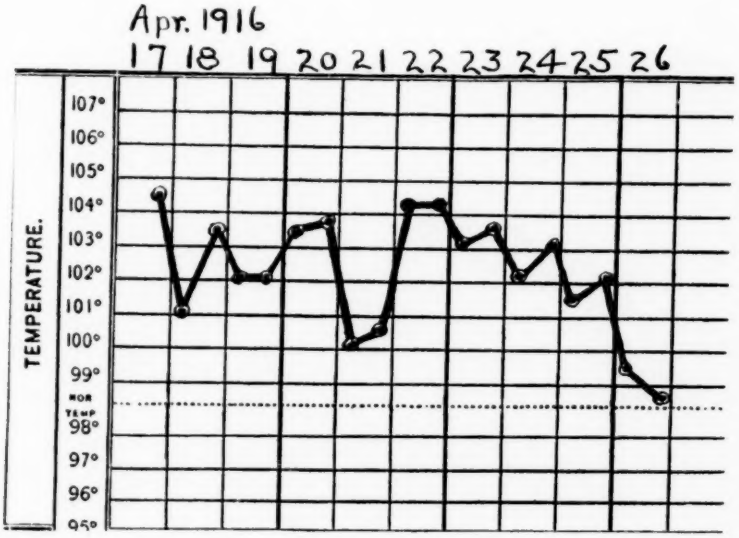
CASE 1915.25

PHYSICAL	MENTAL	SUMMARY
One sister died of tuberculosis. Complains of headaches many years. 1914—Tremor hands, gait unsteady. Albumin, slight trace. Wassermann on blood, negative. 1915, Feb.—Muscular resistance. June—Impaired resonance, sounds diminished, left side. Appetite ravenous. July—Contractures. Death.	Many years has frequently repeated phrases. 1913—Has developed mannerisms and delusions. 1914—Violent. Auditory and visual hallucinations. Mute, resistive, at times active and destructive. Admitted—Untidy, resistive, replied by gestures and mannerisms. Later, restless, denudative, irritable, abusive, profane. Attention poor, irrelevant, disoriented, mistakes identities, memory impaired. Nov.—Spoon fed, then tube fed, negativistic, mute. 1915, Feb.—Mutters and verbigerates, incoherent. May—Restless, noisy, untidy.	Peculiar actions together with headaches for years. At 48 active mental and physical signs which continue till death one year later. Autopsy—Left pleural cavity obliterated. Small area of pneumonia in right upper lobe (probably tuberculous). Lungs fibrous throughout.



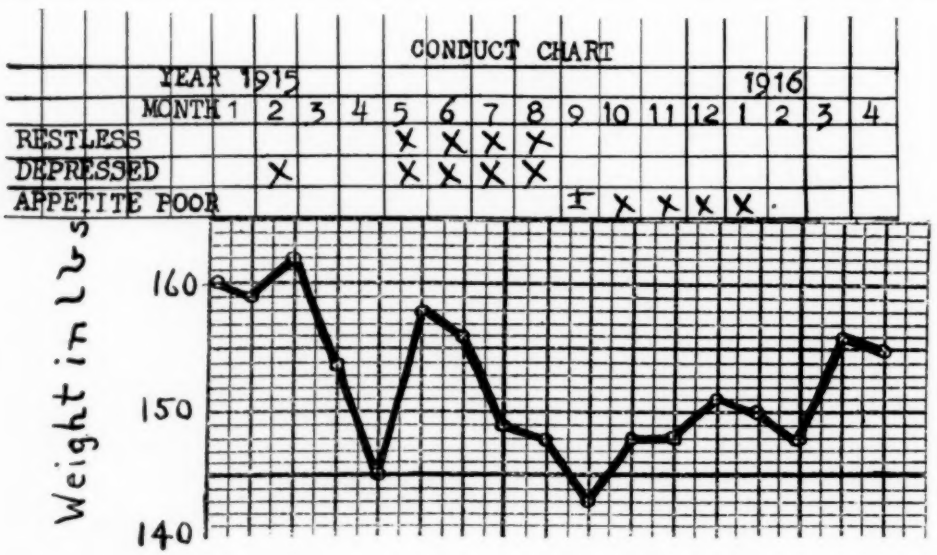
CASE 1916.36

PHYSICAL	MENTAL	SUMMARY
	1887—Moody, sensitive, unreasonable.	At 25 gradual onset with character change. Two years later dangerous. Four years later, hallucinated, homicidal. One to four years later, deluded, incoherent, profane. Seven years later indifferent to hallucinations. Nine years later, ideas of reference, irrelevant.
	1889—Dangerous. Hospital, August to November and discharged.	
	1893—Attempted homicide. Hears name coupled with false and vile statements.	
	1894—"Twenty men murdered every night on the ward." Incoherent. Works.	
	1898—Talks to self but not so profane as formerly.	
1902—Weight, 138 to 145 pounds.	1905—Indifferent, oriented, "voices sound like telephone," profane.	Autopsy—Adhesions right lung externally and to pericardium, and left lung to pericardium.
	1906—Talkative, profane, fair grasp on current events.	
	1914—Hallucinated but "not bothered by them."	
	1915—Irrelevant at times. "People look at him in a peculiar manner and read his thoughts."	
1916—Returned from farm, pneumonia. Weight 121 pounds. Death.		



CASE 1916.37

PHYSICAL	MENTAL	SUMMARY
1910—Easily tired. Nausea, dizzy, weak, dyspneic. Urine negative. 1914—Dysentery. Urine negative. Heart slow, pulse 30 per minute. 1915—Wassermann on blood, negative. 1916, April—Died.	1879—Onset. Untidy, lazy. Masturbates. "Head empty, brains soft." 1882—In Tewksbury. Transferred to Worcester. 1883—Deluded. Tries to burn hair on gas jet. 1886—Talks to self. 1888—Has to be coaxed, irritable. 1905—Has worked at Farm till now. Memory good. Says his delusions were imaginary. Previous visual hallucinations. Claims he got his head jammed between a building and a sleigh. 1910—Works at farm or hospital. Dull. 1912—Apathetic, oriented. Admits previous hallucinations and delusions. 1913—"Picture of depression."	Onset at 28 with mild mental and physical symptoms. Admitted at 31 in dilapidated condition. Improves but remains demented. At 59, signs of vascular trouble. Autopsy—Adhesions of cecum to lateral abdominal wall and of right and left lower lobes to pericardium. Emphysema. Small, white nodule, surface of right kidney. Granular growth from dura separating convolutions in region superior parietal.



LABORATORY METHODS

A MODIFIED HECHT-GRADWOHL TEST FOR THE SERUM DIAGNOSIS OF SYPHILIS*

By W. J. Bruce, New Rochelle, N. Y.

IN reviewing the literature, one is certainly impressed with the many different methods of performing the complement fixation. For years serologists have been trying to devise a satisfactory method of controlling two important factors in this reaction, namely, native complement and native antisheep amboceptor.

Heating serum at 56° C. for 30 minutes destroys the natural complement, but this is a disadvantage, as suggested by Vladimir Busila's[1] work in 1910. He found that sera have two syphilitic antibodies, the one is thermolabile, or destroyed when exposed to a temperature of 56° C., the other thermostable, or unaffected by this degree of heat. These are present in both blood and spinal fluid in varying proportions, and the thermolabile is the first to appear in the blood and the last to disappear under treatment. He also found that when the thermolabile amboceptor is present alone, the Wassermann with heated serum will give a negative result, while with unheated serum a positive result. As the thermolabile antibody often exists alone in nervous, latent, and insufficiently treated syphilis, using the Wassermann technic of performing the test with inactivated serum results in a considerable error in these cases. Noguchi[2] has shown that syphilitic serum heated at 55° C. for 30 minutes loses about one-fourth to one-fifth of its syphilitic antibody.

There are several methods which use the complement in fresh human serum with a fixed amount of amboceptor, but as the native complement is so variable these methods are unreliable unless the serum is titrated for the exact amount of complement present.

Natural antisheep amboceptor is unaffected by heating at 56° C. over a reasonable period, although the complement is eliminated at this temperature. By the addition of sheep red blood corpuscles to inactivated human serum, the native antisheep amboceptor will be absorbed, but this is a tedious procedure, and is seldom carried out routinely. To prevent this native amboceptor entering the test at all, Noguchi[2] used an antihuman, Browning and Mackenzie an antiox, and some workers even produced an antichicken amboceptor.

Hecht and Weinberg[3] in 1909 published a method using the fresh noninactivated human serum and utilizing the native alexin or complement and native antisheep amboceptor. Their method is conducted as follows: Four tubes are used in the test, each tube receiving 0.02 c.c. of fresh patient's serum.

*Read before the St. Anthony's Hospital Clinical Society, Oklahoma City, May 20, 1918.

The antigen used is an alcoholic extract of human heart. Tube No. 1 receives 0.08 c.c. of a 1-50 dilution of antigen, and tube No. 2 receives 0.08 c.c. of a 1-100 dilution, and tube No. 3 receives 0.08 c.c. of a 1-200 dilution, while tube No. 4, which is the serum control does not receive any antigen, but 0.08 c.c. of normal saline. The tubes are placed in the water-bath for ten minutes, and 1 c.c. of a 1 per cent suspension of sheep cells is added to each of the four tubes, and these are reincubated for ten minutes, when the control must show hemolysis; but if it does not, the test is worthless on that particular serum. If a strongly positive acting serum is present there will be complete fixation in all three tubes containing antigen, the control tube showing complete hemolysis. In case the serum is a weakly positive acting one, there will only be complete fixation in the first tube containing the 1-50 dilution of antigen, with the remaining tubes showing hemolysis. A negative serum gives complete hemolysis in all four tubes.

This test is very simple, but unreliable, as it titrates the patient's serum for syphilitic antibody, but not for native complement and amboceptor. The use of such a large arbitrary dose of sheep cells in the presence of such a small amount of serum, leaves this test applicable only to sera of high hemolytic titer. When the control tube does not show any hemolysis, one of two things is at fault, either the patient's serum is low in native hemolysins or an overdose of sheep cells has been added.

Gradwohl[4] saw the possibility of using this test on almost every human serum, as it is estimated that 98 per cent of Americans have some antisheep amboceptor present in sufficient quantities to be utilized. He therefore modified the method of Hecht in such a manner that when the principal test is made it is impossible to have a lack of hemolysis in the serum control tube. A preliminary titration for the exact amount of native hemolysins is first made. His technic is as follows: Place in a rack fourteen small test tubes. The first ten tubes are used to determine the "hemolytic index" of the suspected blood. The last four tubes are used in the actual test. To each of the first ten tubes are added 0.1 c.c. of fresh, unheated patient's serum, then decreasing amounts of normal saline are added to each of these tubes, beginning with 1 c.c. and ending with 0.1 c.c. Next increasing amounts of a fresh 5 per cent suspension of sheep's blood are added, starting with 0.1 c.c. and ending with 1 c.c. Now the rack is placed in the water-bath for thirty minutes. The last tube which shows complete hemolysis constitutes the "hemolytic index" of that serum. If it is tube No. 4 the index is four, because this tube had received 0.4 c.c. of the sheep cell suspension, so therefore, we have obtained an idea as to how much of this suspension is to be added to the last four tubes. The first three tubes, (11, 12, 13) constitute the tubes for the actual test, while the last tube in the rack, (14) serves as the serum control tube. Tubes 11, 12, and 13, receive therefore, the patients' serum, the proper amount of sheep corpuscles (depending on the "hemolytic index"), increasing strengths of antigen, but no complement and no amboceptor. Tube No. 14 receives only patient's serum and sheep corpuscles, but no antigen. One-tenth c.c. of a dilute antigen determined by titration is used in tube No. 11, 0.15 c.c. of antigen in tube No. 12, and 0.2 c.c. in tube No. 13. All the tubes are equalized with normal saline so that each tube contains 0.4 c.c.

of solution. The tubes are agitated and placed in the water for thirty minutes.

The last four tubes are filled at the time of making the additions to the first ten, and are left with them in the water-bath for a half hour for the fixation of the complement. The rack is then taken out and the "hemolytic index" computed. If the index is low, say from 1 to 4, 0.1 c.c. of the sheep cell suspension is added to the last four tubes; if between 5 and 7, 0.15 c.c. is added; and if 8 to 10, 0.3 c.c. is added. But if the index is over 10, the titration for the amount of natural hemolysis is repeated, and if the index falls between 11 and 15, 0.25 c.c. is used, if between 15 and 18, 0.3 c.c. is used, and if between 18 and 20, 0.35 c.c. is used. If a serum has an index below 2, the reaction is regarded as of doubtful value, but if above 2, it is of absolute value. The reaction is read as in the Wassermann, that is, inhibition or noninhibition of hemolysis. If the amount of natural complement or natural antisheep amboceptor is very low, guinea pig serum or immunized rabbit serum can be added in proper proportion ascertained by a preliminary titration. There is no technic given of the method of titrating the antigens for this test.

In a series of 360 persons, Kolmer[5] subjected the sera of each case to both the Wassermann reaction and the Hecht-Gradwohl test, with the same antigens used in each method. His technic is slightly different from that of Gradwohl, as he used fewer tubes for determining the hemolytic index, and instead of adding a certain quantity of sheep cells, according to the sliding scale of Gradwohl, he used one-half the "hemolytic index." The incubation period is also extended from thirty minutes to one hour. The serum is not titrated for syphilitic antibody, and the dose of antigen is 0.2 c.c., and equal to 4 or 5 antigenic units. With this method the same results were obtained in 82 per cent of these cases, 40 per cent were positive in both, 60 per cent were negative with both methods, 12 per cent more positive results were obtained with the Hecht-Gradwohl than with the Wassermann test.

In this laboratory a Wassermann and a Hecht-Gradwohl control is made on every specimen of serum, provided there is a sufficient quantity of serum, and native hemolysins. The routine followed is so arranged that the control test will not interfere with the work of setting up the Wassermann test. A sufficient sheep cell suspension is made to allow 8 c.c. for each specimen to be tested. The human serum is freed of red blood cells, and a certain amount is placed in a rack for inactivation, and the remaining serum is placed in another rack for the Hecht control test. The antigen is now diluted to the proper strength.

The titrations of guinea pig serum and amboceptor for the Wassermann test is next made and placed in the water-bath, and the racks of patient's sera that have already been prepared are placed in a water-bath to inactivate. Work can now be commenced on the Hecht-Gradwohl test, and usually this test is ready to be incubated before either the hemolytic titrations, or the Wassermann sera are ready to be taken out. During this time the sera are prepared, and the titrations for the Wassermann are being made, the Hecht-Gradwohl test is in the water-bath, allowing work on the Wassermann test to commence immediately, and with no loss of time.

The following technic has given the best results in our hands. The specimen is collected within 48 hours of performing the test. About 8 or 10 c.c. of blood is drawn into a sterile container and allowed to clot at room temperature. The clot is now separated from the test tube and the specimen placed in the refrigerator overnight. The following morning the tube is centrifuged and the clear serum pipetted off into a sterile test tube, and again placed in the refrigerator until the test is made. Sera treated this way have shown a fairly high "hemolytic index" after 72 hours. Although 8 per cent of our sera failed to give any hemolysis, many of these were collected and sent to the laboratory by mail, and therefore, did not receive the proper attention to prevent the deterioration of the native complement. No attempt was made to add any amboceptor, or replace the complement in these seras.

SHEEP CELL SUSPENSION

Fresh sheep blood is used. This is washed with normal saline until the supernatant fluid is albumin negative with the heat and acetic acid test. A 3 per cent suspension of washed cells is made in sufficient quantity to complete the test on all the sera. As each test requires about 8 c.c. of this suspension, 100 c.c. will be sufficient for 12 different sera. The cell suspension used to titrate for the hemolytic index must be used in the final test.

ANTIGEN

Organic extracts are capable of hemolyzing red blood cells due to hemotoxic action of alcohol and lipoids. For this reason the antigen must be titrated for its hemolytic unit. Ten test tubes are placed in a rack and the following amounts of a 1-10 dilution of antigen are added, i. e., 0.2, 0.4, 0.6, 1.0, 1.2, 1.5, 2.0, 2.5, 3.0 c.c. Each tube now receives 0.5 c.c. of 3 per cent cell suspension, and the volume brought up to 3.5 c.c. with normal saline. These are incubated for one hour at 38°C. and the first tube that shows the slightest hemolysis is considered the hemolytic unit.

ANTICOMPLEMENTARY TITRATIONS

Serum is obtained from three healthy nonsyphilitic Wassermann negative persons. These sera are pooled and titrated for the hemolytic index.

Twelve test tubes are racked up and each tube receives 0.1 c.c. of this pooled serum with varying amounts of a 1-10 dilution of antigen ranging from 0.1 c.c. to 2.0 c.c. A tube containing serum but no antigen is used as a serum control. All the tubes are brought up to a volume of 2.5 c.c. (less one-half the hemolytic index) with normal saline, and incubated in the water-bath for one hour. One-half the known hemolytic index is then added and reincubated for another hour. The first tube that shows the slightest inhibition of hemolysis is recorded as the anticomplementary unit. The serum control tube must show complete hemolysis.

ANTIGENIC TITRATIONS

Pooled serum from three syphilitic Wassermann positive patients is used. The hemolytic index is determined, and 0.1 c.c. of this serum is added to twenty

test tubes. Each tube receives varying amounts of a 1-10 dilution of antigen ranging from 0.01 c.c. to 0.2 c.c. The hundredths of antigen were diluted so that 0.1 c.c. equaled 0.01 c.c. of a 1-10 dilution. A serum control is also used. The remainder of the test is conducted as for the anticomplementary unit. After the tubes are reincubated they are placed in the refrigerator overnight, and the first tube showing complete inhibition of hemolysis is considered the antigenic unit. The antigen used in our work was the protein free, reprecipitated, acetone insoluble lipoids, prepared according to Noguchi. Four or five antigenic units was the dose used in the principal test, and this amount was less than one-twentieth the anticomplementary unit.

TECHNIC OF THE TEST

Twelve tubes are placed in a rack and all these receive 0.1 c.c. of the suspected noninactivated serum. To the first ten tubes varying amounts of a 3 per cent suspension of washed sheep cells are added, beginning with 0.2 c.c. and ending with 1.1 c.c. Normal saline is now added to bring the volume of these ten tubes up to 2.0 c.c. Tube No. 11 is the antigen tube, and receives the proper dose of antigen, as determined by titration, while tube No. 12 is the serum control and does not receive any antigen. Sufficient normal saline is added to these two tubes to make a volume of 0.5 c.c. The racks are placed in the water-bath for one hour at 38°C. and shaken occasionally. At the end of this time the racks are removed and the last tube which shows complete hemolysis is considered the hemolytic index. At this point the first ten tubes are discarded, and one-half of the hemolytic index is added to each of the two remaining tubes. These tubes are thoroughly shaken and reincubated in the water-bath for another hour, and placed in the refrigerator overnight.

When a negative result is obtained, hemolysis usually occurs within the first ten or fifteen minutes, and if a positive reaction is present, we have a picture similar to a four-plus positive Wassermann. Only in cases that are Wassermann negative, and are receiving thorough treatment, do we get a tube showing partial hemolysis. It is important that all the tubes be thoroughly shaken every ten or fifteen minutes during incubation.

Sellards and Minot[6] published, in 1916, a series of 134 cases, in which they found only 14 sera, containing two or more units of natural antisheep amboceptor, and were unable to offer an explanation for the lack of hemolysis.

If these workers used fresh active serums, their trouble was undoubtedly due to a too heavy sheep cell suspension. Gradwohl has constantly obtained a positive Hecht-Gradwohl when the Wassermann was positive, and 15 per cent more positives than with the Wassermann reaction. Kolmer's figures are 18 per cent more true positive results with an acetone antigen than with the Wassermann test. If the blood was collected within 48 hours of making the test, he found there was sufficient native complement and native antisheep amboceptor present to conduct the test. In our series of 608 sera 8 per cent failed to hemolyze any sheep corpuscles. The Wassermann test performed with active and inactivated sera and the Hecht-Gradwohl, with the modification given above

was paralleled on 532 sera. Positive Wassermann with positive Hecht-Gradwohl tests were obtained on 105 or 20.6 per cent; negative Wassermann and negative Hecht-Gradwohl tests were obtained on 395 sera or 74.2 per cent. Positive Hecht-Gradwohl tests and negative Wassermann tests were obtained on 32 or 5.7 per cent of these cases.

While these figures are considerably lower than either those of Gradwohl or Kolmer, yet this difference can probably be explained by the method used in the Wassermann test. In our Wassermann technic we use both inactivated and noninactivated serum and even if there is an absence of fixation with heated serum, and present with unheated serum the test is reported as positive. If you compare our results with a Wassermann, made with heated serum alone, our results would correspond with those of the former writers.

CONCLUSIONS

In primary syphilis the modified Hecht has always shown up positive in from one to two weeks earlier than the Wassermann. A positive result can usually be obtained in from one to two weeks after the initial lesion with this test. In treated cases the Hecht-Gradwohl has always been the last to disappear. This test has its greatest value as a serological control in the treatment of syphilis, and in the interpretation of a weakly positive or "borderline" Wassermann reaction. It must be conducted with a properly standardized antigen, the proper dose of sheep cells, and fresh noninactivated sera. With the technic just described we have not found a single case in which the Wassermann was positive and the Hecht-Gradwohl negative. Although this test is more delicate than the Wassermann reaction in the serological diagnosis of syphilis, yet it can not be utilized on every serum due to the lack of native hemolysins, and must therefore serve the purpose of a control test.

The observations of Sellards and Minot have not been confirmed.

I am deeply indebted to Dr. O. J. Walker for his many suggestions and able assistance in the preparation of this paper.

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A SIMPLE DISTILLING APPARATUS*

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A SIMPLE, inexpensive and rapid device for obtaining distilled water has been devised. The only essential is steam pressure.

The main pipe conveying the live steam to the laboratory runs along the wall about six feet from the floor. A three-quarter inch pipe (A) is led vertically downward from the main pipe to several inches from the bottom of the sink basin and then continued transversely for about nine inches where it opens into the basin. At about six inches from the angle, a "T" connection

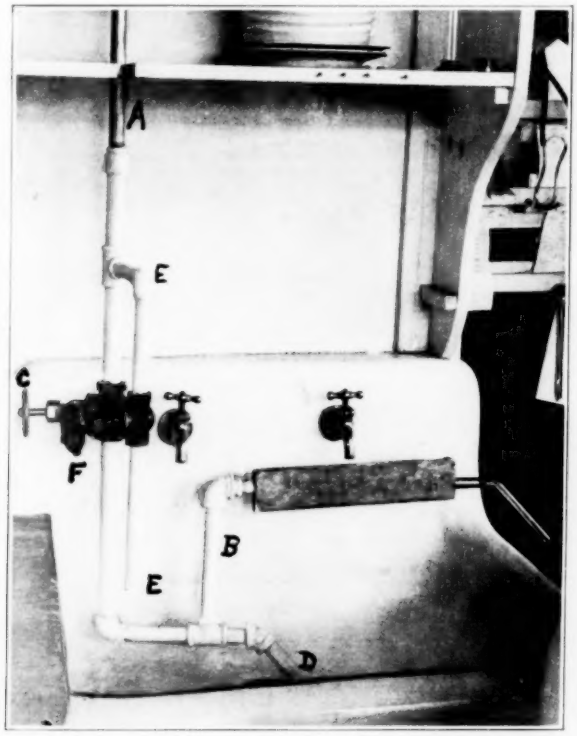

Fig. 1.

is inserted and a half inch pipe (B) extended upward for about nine inches more or less depending upon the height of the water faucet. To the end of this pipe is attached an "L" connection to which the distilling apparatus is screwed when its use is desired, at other times it is disconnected. This vertical nine-inch pipe is bent either slightly forward or backward so that when the distilling tube is attached, it is in line with the cold water faucet (Fig. 1).

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The distilling apparatus (Fig. 2) consists of an ordinary nickel plated or copper tube about sixteen inches long to which is soldered a cradle made of 24 gauge metallic sheet iron. When distilled water is wanted, a valve (C) (Fig. 1) attached to the extension pipe is opened so that a heavy flow of steam escapes from the distilling tube. The cold water is then allowed to run and kept overflowing the cradle; the water within the cradle is constantly cool. The steam at once condenses and distilled water is obtained. By means of a rubber stopper, a bent glass tube may be inserted into the outer end of the distilling tube for carrying the distilled water to a retainer.

A gallon of water is obtained in about forty minutes. A moderate quantity of steam escapes from the lower opening of the pipe (D) into the sink. This can be obviated by placing a moist towel over this exit. The distilling apparatus was purposely not led off directly from the main pipe extending down-

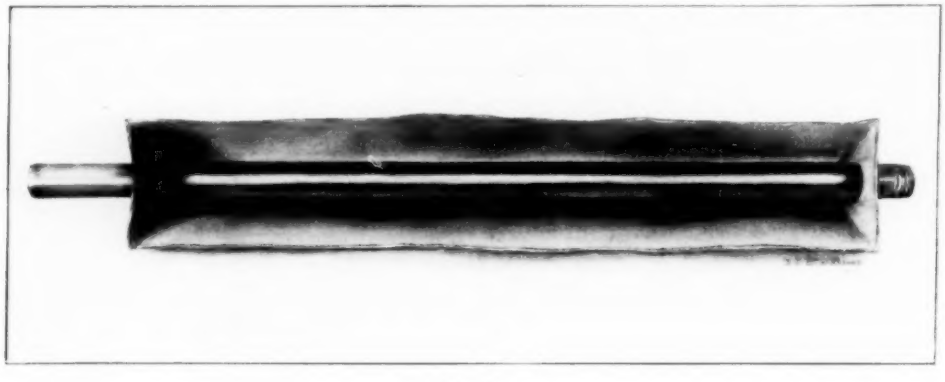

Fig. 2.

ward, so that if any water is condensed on the way from the engine house, it may escape into the sink from the lower exit and only steam will flow upward through the "T" extension. The additional outlet (E) seen in Fig. 1 coming off from the main vertical extension, has nothing to do with the distilling device. It is simply a steam outlet for purposes of disinfection. This extension has its separate valve (F).

For those accustomed to obtain distilled water by means of the ordinary house still, heated by a Khotal burner, this appliance will undoubtedly be of aid. Even the Stokes Automatic Still does not give as much water per hour as does this simple device. It is especially appreciated by those who are so insistent upon the use of absolutely freshly distilled water for Arsphenamine administration.

The Journal of Laboratory and Clinical Medicine

VOL. IV. JANUARY, 1919 No. 4

Editor-in-Chief: VICTOR C. VAUGHAN, M.D.
Ann Arbor, Mich.

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Influenza and Pneumonia at Brest, France

FROM April 1 to July 31, 1918, a mild epidemic of influenza and pneumonia prevailed at Brest and in that vicinity. During this time there were admitted to our Naval Base Hospital at Brest, 50 cases of influenza, 26 of whom developed pneumonia, with two deaths. During the same period the French military, civil and naval authorities reported 4,838 cases of influenza, with 688 hospital admissions and 53 deaths. In one station among 1,018 young French recruits, 688 were admitted to the hospital and 49 deaths occurred. The mildness of this outbreak was in sharp contrast to what occurred later. About August 22 a more violent outbreak occurred, and from this date to September 15 there were 1,350 hospital admissions with 370 deaths. However, influenza reached its greatest violence in September, and the pneumonia followed in October. During these months 458 cases of influenza were admitted to our Naval Hospital, with 171 developing pneumonia and 65 deaths. This means a case fatality of 38 per cent for pneumonia. The death rate among cases of pneumonia originating on shore at Brest was 38 per cent, while among those taken from transports it was 48 per cent.

The influenza was characterized by a sudden onset, marked prostration, rapid rise of temperature to 103° to 105°, headache and myalgia, and in severe cases a cloudy skin. The leucocyte count was low, while that of the lymphocytes was relatively high. Throat symptoms were not marked notwithstanding the

fact that in the region of Brest, primary colds are commonly marked by early pharyngitis and even by laryngitis, and sometimes by tracheitis. Epistaxis was frequent. But few cases escaped bronchitis, which appeared in many instances after the temperature had dropped to normal and patients were apparently convalescing. Two cases of influenza showed symptoms strongly suggestive of appendicitis. In only one case was there a definite gastrointestinal form of grippe, showing marked nausea, vomiting, high temperature and severe diarrhea. This patient, after his temperature had reached normal and his diarrhea disappeared, was suddenly seized with severe pain in his right side. His temperature rose to 105°, the leucocyte count which was only 5,000 during his early attack rose to 14,200, and distinct signs of involvement of the right lower lobe appeared. This case finally ended in recovery.

In a large percentage of the cases pneumonia was at first distinctly lobular, but the areas of involvement soon became multiple and of wide extent. Bacteriological study demonstrated the presence of pneumococci, Type I, both in the sputum during life and in the heart blood after death. Many cases were characterized by the usual bloody sputum and some showed a decided increase in leucocytes, though few reached the large numbers usually found in pneumococcus pneumonias. Most cases showed a bronchitis present on both sides and accompanied by cyanosis and extreme dyspnea.

The sputum varied from plain mucopurulent to typical pneumococcic. The influenza bacillus was found in one of the specimens only. In another there was found a pure culture of staphylococcus. These findings were confirmed by securing pure cultures directly from the lungs postmortem. The conclusion was that the disease was a real pneumococcus infection complicated, however, in some instances, with bronchitis in an exaggerated form. In one case hemolytic streptococci were found in the blood during life, and on postmortem examination pure cultures of this organism were obtained from the heart blood in seven cases. Throat cultures made upon admission showed no hemolytic streptococci. In the French hospital at Brest during the same period, of 64 blood cultures, 47 were negative and 11 gave such a varied growth as to suggest contamination. In 6 cases, all severely ill, streptococci were found; in 2 this organism was associated with a diplococcus. Six lung punctures gave pure cultures of streptococci in 4 instances, while 2 were sterile. At the French hospitals the sputum showed streptococcus infrequently, but these organisms were recovered in all cases coming to autopsy, and cultures from the heart blood of those dead of influenza contained streptococci in all instances. In one case where the autopsy was delayed streptococci were associated with a septic vibrio. French observers said that this streptococcus presents the biologic properties of streptococci in general, only occasionally were they of the hemolytic type, and they lay stress on the fact that it is highly virulent for man. This was demonstrated accidentally when one of the French surgeons, who was infected in making a pleurotomy on a case of grippe, died of streptococcus septicemia.

Sixty-nine autopsies were performed at the United States Naval Base Hospital No. 5 on bodies dead of influenza during the last two months. The pathologist thinks that the cases studied here fall among the lobar type rather than

under the massive bronchopneumonia type. From clinical experience alone one would have expected to have a larger number of bronchopneumonias, but recoveries among this type of cases were perhaps proportionately larger.

Masks appeared to be of value in limiting the transmission of influenza from patient to patient as well as from patient to nurse and to hospital corpsmen. Masks are not recommended for pneumonia patients, as they interfere with the breathing and are rarely kept in place. The beds in the hospitals were converted into cubicles, and it is believed that this procedure was of service.

The conclusion of this report, which is made by Lieutenant Commander James E. Talley, M. C., U. S. N. R. F., is stated as follows:

"A very severe epidemic of influenza has just ended in which over 10 per cent of the cases appearing at this station developed pneumonia which clinically usually developed as a lobular pneumonia but tended to involve wide areas. Influenza bacilli were demonstrated but rarely. This we believe has been a common experience in France. However, the possibility that a filterable virus is the cause of influenza is not yet excluded, and one is just beginning to hear more of the filterable coccoid form of the influenza bacillus. There seems good reason to believe that streptococci and various pneumococci are often secondary invaders, because in the same epidemic the same workers in different places have found different bacteria predominating. For instance, one hears that Dr. Martin, the subdirector of the Pasteur Institute, who spent some weeks here when streptococci seemed to be most active, now finds pneumococci the commonest bacteria in his material, whereas in other parts of Paris streptococci still predominate. Here in the local French hospitals, where earlier one found only streptococci, many pneumococci are now seen."

—*V. C. V.*

Influenza in Camp Custer

THIS report was made by Major John S. Billings. The epidemic made its appearance at Camp Custer on September 23. It followed an increased prevalence of coughs, colds, tonsillitis, bronchitis, pharyngitis, etc. The total strength of the command is that of October 1, 1918, and is given as 39,678. It is a question whether the colds, etc., referred to as having occurred before September 23 were or were not cases of influenza. At least on and after September 23 these cases were diagnosed as influenza. From September 23 the number of cases increased in fairly regular geometrical proportions, reaching its maximum on October 2 when 1,227 cases were admitted. The crest of the wave held for about four days, when a fall followed. The regression was steady and continuous, the number falling below 100 on October 14, below 50 on October 20, below 20 on October 24, and below 10 on October 29. The epidemic was declared closed on November 3.

The epidemic appeared in the 78th Infantry first, which numbered 3,561. The general sanitary condition of this command was excellent in all respects save one. All organizations were instructed to boil their mess kits, the order

being issued in August, 1918. Through some confusion and delay the 78th Infantry did not begin sterilizing their mess kits until September 26.

The 160th Depot Brigade numbered 14,048, making more than one-third of the entire command. The units of this brigade were widely scattered throughout the camp and under varying housing conditions. Their make-up also differed—some consisting of negro troops, others consisting largely of venereal cases.

The 41st Field Artillery had the greatest number of cases in proportion to its strength (543 per 1,000). Major Billings says that this may have been due to one of two things: (a) on October 5 a detail of 100 men from this organization was sent to the Base Hospital Annex for night work, returning to their barracks the next day. On October 6 a new detail of 100 men did the same thing, and 35 on October 7. The morbidity increased from 14 cases on October 5 to 135 on October 6; (b) this organization had among its sick the highest proportion of men of less than two months in the service.

Field Artillery No. 42 came next with a morbidity of 509 per 1,000. No reason could be found as the regiment was located in a very desirable part of the camp. Its percentage of new men was low and special precautions were taken to quickly isolate new cases. No man with a temperature over 100° was detailed to fatigue duty. The 10th Infantry had the lowest morbidity (162 per 1,000) with 30 per cent of new men. Next in order came the Sanitary Train with 163 per 1,000, and 57 per cent of new men.

Of the total of 10,421 cases, 4,668 were admitted direct to the Base Hospital, 5,457 to the particular Regimental Hospital, and 296 were sent to quarters.

It was the opinion of the organization surgeons that typical cases of influenza were seen as early as September 22, and while the severity of the cases became greatly intensified, the change was one of degree only. However, at the Base Hospital it was felt that few cases of true influenza were admitted prior to September 27. The entire symptom-complex seemed to change on that day, and the cases admitted to the hospital from then on were of a very different and more severe type. The earlier cases were recorded as simple bronchitis and pharyngitis of no great severity, the majority soon recovering. The epidemiologist says that he can give no information as to which group of observers was correct, but consideration of the records would make it seem unlikely that there were two distinct diseases for the following reasons:

1. No cases of simple bronchitis or pharyngitis were reported after September 29, although on the four preceding days there were 577 cases of bronchitis and 144 of pharyngitis.

2. As far as could be ascertained, none of the patients admitted prior to September 27 returned later suffering from the more severe type of illness.

3. There was no further sharp increase in the number of cases.

4. There was no sudden increase in the fatality of the cases occurring after that date. However, he says it is not only possible, but probable, that one or more new infections were superadded to the original infection at the time mentioned above.

5. Cases of the milder type returning to quarters from hospitals, while seem-

ingly immune to infection with the more severe type of the disease, were followed by the development of cases of the latter type. One instance occurred in the 14th Ammunition Train, where J. L. was sent to the Base Hospital on September 20. He was discharged still coughing, on September 27, as having suffered from bronchitis. Believing the case to have been one of influenza, the surgeon had him cubicled in the corner of the barracks, and warned him to keep away from other men; but two cases developed in that corner of the barracks on September 29, with 20 more cases in the next three days.

6. There was a sharp increase in the number of pneumonia cases coincident with the rise in the influenza cases, and the two curves continued to correspond.

The most noteworthy symptoms were as follows: marked prostration, almost comatose somnolence, dull expression, flushed and often cyanotic face, relative absence of cough, and marked congestion of the mucous membranes, congested eyes, red throat, hemoptysis and epistaxis. The last-mentioned symptom was noted in 30 per cent of the cases in one command. The congestion of the conjunctiva and sclera was so characteristic that a diagnosis could be made even at a distance.

It was observed in many cases that individuals admitted with high temperature would often improve quite markedly after twenty-four hours and walk to the lavatory, but in a few days their condition would grow rapidly worse with the development of pneumonia. On the other hand, cases with moderate or low temperature would improve more slowly, but more continuously, and less frequently develop pneumonia. Although the onset of the attacks was sharp and sudden, yet an initial chill, or one on the development of pneumonia, was rarely or never observed. No rashes, skin eruptions, or other exanthems appeared.

The Streptococcus hemolyticus was present in 75 per cent of the cultures, the Bacillus influenzæ in about 1 per cent. The Bacillus influenzæ was found in only 8 per cent of the cases of influenza in the prepneumonia stage, as against 34 per cent of the Streptococcus hemolyticus, and 12 per cent of the pneumococcus. After the development of pneumonia the Bacillus influenzæ was found in 4 per cent, usually associated with the streptococcus, while the streptococcus was found in 26 per cent.

Pathologically the cases were pronounced bronchopneumonia, and it is believed that the lesions were due principally to the streptococcus. There was marked leucopenia.

Following the epidemic there was an increase in cases of tonsillitis, erysipelas and otitis. Empyema, which had occurred rarely during the summer, developed in 43 cases of pneumonia after October 17. There were 30 cases of otitis media at the Base Hospital during the month of October.

Sixty-four per cent of the men had been in the service only two months.

The 41st Field Artillery showed the greatest relative percentage, and the Quartermaster Corps the least. The increased prevalence of the disease in the first two months after enlistment has been ascribed to the larger proportion of unfit men in the service at that period; that is, unfit men who had not been weeded out.

Most surgeons reported that the rurals in their command suffered more

largely than urbans. It was thought by some that the crowding, due to a series of lectures on venereal diseases just about the time the epidemic appeared, gave opportunity for the wide dissemination of the contagion.

Three thousand six hundred thirty-three of the command were in tents. The morbidity per thousand in these was 129. Thirty-six thousand fifty-five were in barracks. The morbidity per thousand among those was 275. At first glance the lower morbidity of those in tents is striking. Going further into the matter, however, it is found that the entire morbidity of the Quartermaster Corps was very low.

Of the Depot Brigade, 2,881 were in tents, with a morbidity of 128 per thousand, while 3,824 were in barracks, with a morbidity of 134 per thousand.

During the month of September and the first part of October, the weather was splendid. Before the beginning of the epidemic all organizations in the Division were doing intensive work. The ration was liberal, the average consumption per man being between 4,000 and 5,000 calories.

One of the larger organizations did not promptly observe the regulations requiring that all mess kits and table equipment be properly sterilized. This may have played a part in the epidemic, and may be the reason the disease appeared so early and spread so rapidly in this particular organization. It was largely felt that the two blankets supplied were not enough, and that the men were cold at night.

Camp Custer is about five miles from Battle Creek, which has a population of about 32,000. The first cases in Battle Creek were reported on September 30. There was a sharp increase on and after October 3. It is improbable that Camp Custer owed its outbreak to Battle Creek.

—*V. C. V.*